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IONS.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	287510
CHANNEL.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	972996
CHANNELS.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	472731
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<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
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<u>L11</u>	ih ion channel	1	<u>L11</u>
<u>L10</u>	juelich-arnd baumann.in.	0	<u>L10</u>
<u>L9</u>	juelich-wolfgang-bonigk.in.	0	<u>L9</u>
<u>L8</u>	juelich-renate-gauss.in.	0	<u>L8</u>
<u>L7</u>	dormagen-alexander-scholten.in.	0	<u>L7</u>
<u>L6</u>	aachen-reinhard-seifert.in	0	<u>L6</u>
<u>L5</u>	aachen-benjamin-kauup.in	0	<u>L5</u>
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<u>L4</u>	juelich-renate-gauss.in.	0	<u>L4</u>
<u>L3</u>	dormagen-alexander-scholten.in.	0	<u>L3</u>
<u>L2</u>	aachen-reinhard-seifert.in	0	<u>L2</u>
<u>L1</u>	aachen-benjamin-kauup.in	0	<u>L1</u>

END OF SEARCH HISTORY

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FILE 'MEDLINE'
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=> s ih ion channel or ih channel
L1 127 IH ION CHANNEL OR IH CHANNEL

=> dup rem 11
PROCESSING COMPLETED FOR L1
L2 68 DUP REM L1 (59 DUPLICATES REMOVED)

=> d 12 ibib abs 1-68

L2 ANSWER 1 OF 68 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002365681 MEDLINE
DOCUMENT NUMBER: 22103692 PubMed ID: 12093909
TITLE: Assessing the role of ***Ih*** ***channels*** in synaptic transmission and mossy fiber LTP.
AUTHOR: Chevalyre Vivien; Castillo Pablo E
CORPORATE SOURCE: Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Jul 9) 99 (14)

9538-43. Journal code: 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20020809
Entered Medline: 20020808

AB Hyperpolarization-activated nonselective cation channels (***Ih*** ***channels***) play an important role in the control of membrane excitability and rhythmic neuronal activity. The functional relevance of presynaptic ***Ih*** ***channels*** in regulating synaptic function, however, is not well established. Recently, it has been proposed [Mellor, J., Nicoll, R. A. & Schmitz, D. (2002) Science 295, 143-147] that presynaptic ***Ih*** ***channels*** are necessary for hippocampal mossy fiber long-term potentiation (LTP). This observation challenges an alternative model that suggests presynaptic forms of LTP are caused by a direct modification of the transmitter release machinery. Here, we assess the role of Ih in hippocampal mossy fiber LTP as well as cerebellar parallel fiber LTP, forms of potentiation that share common mechanisms. Our results show that after Ih blockade neither mossy fiber LTP nor parallel fiber LTP are affected. Furthermore, Ih does not significantly modify basal excitatory synaptic transmission in the hippocampus, whereas the organic Ih blockers ZD7288 and DK-AH 269 induce a large Ih-independent depression of synaptic transmission. In summary, our results indicate that Ih-mediated persistent changes in presynaptic excitability do not underlie presynaptic forms of LTP.

L2 ANSWER 2 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:380003 BIOSIS
DOCUMENT NUMBER: PREV200200380003
TITLE: Dendritic resonance in rat neocortical pyramidal cells.
AUTHOR(S): Ulrich, Daniel (1)
CORPORATE SOURCE: (1) Institute of Physiology, University of Bern, Buhlplatz

5, 3012, Bern: Ulrich@pyl.unibe.ch Switzerland
SOURCE: Journal of Neurophysiology (Bethesda), (June, 2002) Vol.

87, No. 6, pp. 2753-2759. <http://jn.org>; <http://www.jn.org>. print. ISSN: 0022-3077.

DOCUMENT TYPE: Article
LANGUAGE: English
AB Dendritic integration of synaptic signals is likely to be an important process by which nerve cells encode synaptic input into spike output. However, the response properties of dendrites to time-varying inputs are largely unknown. Here, I determine the transfer impedance of the apical dendrite in layer V pyramidal cells by dual whole cell patchclamp recordings in slices of rat somatosensory cortex. Sinusoidal current waveforms of linearly changing frequencies (0.1-25 Hz) were alternately injected into the soma or apical dendrite and the resulting voltage oscillations recorded by the second electrode. Dendrosomatic and somatodendritic transfer impedances were calculated by Fourier analysis. At near physiological temperatures (Tappx35degreeC), the transfer impedance had a maximal magnitude at low frequencies (fresappx6

Hz). In addition, voltage led current up to apprx3 Hz, followed by a current lead over voltage at higher frequencies. Thus the transfer impedance of the apical dendrite is characterized by a low-frequency resonance. The frequency of the resonance was voltage dependent, and its strength increased with dendritic distance. The resonance was completely abolished by the ***Ih*** ***channel*** blocker ZD 7288. Dendrosomatic and somatodendritic transfer properties of the apical dendrite were independent of direction or amplitude of the input current, and the responses of individual versus distributed inputs were additive, thus implying linearity. For just threshold current injections, action potentials were generated preferentially at the resonating frequency. I conclude that due to the interplay of a sag current (Ih) with the membrane capacitance, layer V pyramids can act as linear band-pass filters with a frequency preference in the theta frequency band.

L2 ANSWER 3 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:187551 BIOSIS
DOCUMENT NUMBER: PREV200200187551
TITLE: ***Ih*** ***channels*** contribute to the different functional properties of identified dopaminergic subpopulations in the midbrain.
AUTHOR(S): Neuhoff, Henrike; Neu, Axel; Liss, Birgit; Roeper, Jochen

(1)
CORPORATE SOURCE: (1) Medical Research Council, Anatomical Neuropharmacology Unit, Oxford University, Mansfield Road, Oxford, OX1 3TH: jochen.roeper@pharm.ox.ac.uk UK

SOURCE: Journal of Neuroscience, (February 15, 2002) Vol. 22, No. 4, pp. 1290-1302. <http://www.jneurosci.org/>. print. ISSN: 0270-6474.

DOCUMENT TYPE: Article
LANGUAGE: English
AB Dopaminergic (DA) midbrain neurons in the substantia nigra (SN) and ventral tegmental area (VTA) are involved in various brain functions such as voluntary movement and reward and are targets in disorders such as Parkinson's disease and schizophrenia. To study the functional properties of identified DA neurons in mouse midbrain slices, we combined patch-clamp recordings with either neurobiotin cell-filling and triple labeling confocal immunohistochemistry, or single-cell RT-PCR. We discriminated four DA subpopulations based on anatomical and neurochemical differences: two calbindin D28-k (CB)-expressing DA populations in the substantia nigra (SN/CB+) or ventral tegmental area (VTA/CB+), and respectively, two calbindin D28-k negative DA populations (SN/CB-, VTA/CB-). VTA/CB+ DA neurons displayed significantly faster pacemaker frequencies with smaller afterhyperpolarizations compared with other DA neurons. In contrast, all four DA populations possessed significant differences in ***Ih*** ***channel*** densities and ***Ih*** ***channel***-mediated functional properties like sag amplitudes and rebound delays in the following order: SN/CB- fwdarw VTA/CB- fwdarw SN/CB+ fwdarw VTA/CB+. Single-cell RT-multiplex PCR experiments demonstrated that calbindin but not calretinin expression is associated with differential ***Ih*** ***channel*** densities. Only in SN/CB- DA neurons, however, ***Ih*** ***channels*** were actively involved in pacemaker frequency control. In conclusion, diversity within the DA system is not restricted to distinct axonal projections and differences in synaptic connectivity, but also involves differences in postsynaptic conductances between neurochemically and topographically distinct DA neurons.

L2 ANSWER 4 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

ACCESSION NUMBER: 2002:428994 BIOSIS
DOCUMENT NUMBER: PREV200200428994
TITLE: Convergent and reciprocal modulation of a leak K+ current

and Ih by an inhalational anaesthetic and neurotransmitters in rat brainstem motoneurons.
AUTHOR(S): Sirois, Jay E. (1); Lynch, Carl, III; Bayliss, Douglas A.
CORPORATE SOURCE: (1) Department of Pharmacology, University of Virginia,

5017 Jordan Hall, Box 448, Charlottesville, VA, 22908: jes8q@virginia.edu USA

SOURCE: Journal of Physiology (Cambridge), (15 June, 2002) Vol.

541, No. 3, pp. 717-729. <http://uk.cambridge.org/journals/p> hyl. print. ISSN: 0022-3751.

DOCUMENT TYPE: Article
LANGUAGE: English
AB Neurotransmitters and volatile anaesthetics have opposing effects on

motoneuronal excitability which appear to reflect contrasting modulation of two types of subthreshold currents. Neurotransmitters increase motoneuronal excitability by inhibiting TWIK-related acid-sensitive K+ channels (TASK) and shifting activation of a hyperpolarization-activated cationic current (Ih) to more depolarized potentials; on the other hand, anaesthetics decrease excitability by activating a TASK-like current and inducing a hyperpolarizing shift in Ih activation. Here, we used whole-cell recording from motoneurons in brainstem slices to test if neurotransmitters (serotonin (5-HT) and noradrenaline (NA)) and an anaesthetic (halothane) indeed compete for modulation of the same ion channels - and we determined which prevails. When applied together under current clamp conditions, 5-HT reversed anaesthetic-induced membrane hyperpolarization and increased motoneuronal excitability. Under voltage clamp conditions, 5-HT and NA overcame most, but not all, of the halothane-induced current. When Ih was blocked with ZD 7288, the neurotransmitters completely inhibited the K+ current activated by halothane; the halothane-sensitive neuro-transmitter current reversed at the equilibrium potential for potassium (EK) and displayed properties expected of acid-sensitive, open-rectifier TASK channels. To characterize modulation of Ih in relative isolation, effects of 5-HT and halothane were examined in acidified bath solutions that blocked TASK channels. Under these conditions, 5-HT and halothane each caused their characteristic shift in voltage-dependent gating of Ih. When tested concurrently, however, halothane decreased the neurotransmitter-induced depolarizing shift in Ih activation. Thus, halothane and neurotransmitters converge on TASK and ***Ih*** ***channels*** with opposite effects; transmitter action prevailed over anaesthetic effects on TASK channels, but not over effects on Ih. These data suggest that anaesthetic actions resulting from effects on either TASK or hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in motoneurons, and perhaps at other CNS sites, can be modulated by prevailing neurotransmitter tone.

L2 ANSWER 5 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 2002:197203 BIOSIS
DOCUMENT NUMBER: PREV200200197203
TITLE: Temporal synaptic tagging by Ih activation and actin: Involvement in long-term facilitation and cAMP-induced synaptic enhancement.

AUTHOR(S): Beaumont, Vahri (1); Zhong, Ning; Froemke, Robert C.; Ball,

Robin W.; Zucker, Robert S.
CORPORATE SOURCE: (1) Division of Neurobiology, MRC Laboratory of Molecular

Biology, Hills Road, Cambridge, CB2 2QH: vahri@mrc-lmb.cam.ac.uk UK

SOURCE: Neuron, (February 14, 2002) Vol. 33, No. 4, pp. 601-613.

<http://www.neuron.org/>. print. ISSN: 0896-6273.

DOCUMENT TYPE: Article
LANGUAGE: English
AB Presynaptic ***Ih*** ***channels*** become activated during a tetanus through membrane hyperpolarization resulting from Na+ accumulation and electrogenic Na+/K+ exchange. Ih activation is obligatory for inducing long-term facilitation (LTF), a long-lasting synaptic strengthening. cAMP-induced synaptic enhancement also requires Ih activation, and both processes are sensitive to actin depolymerization. Other mechanisms are responsible for expression of the responses. Once initiated, continued response to cAMP is Ih and actin independent. Moreover, LTF-induced activation of Ih renders subsequent cAMP enhancement insensitive to both Ih blockers and actin depolymerization. This actin-stabilized "temporal synaptic tagging" set by Ih activation is prolonged when Ih is activated concurrent with an elevation in presynaptic calcium concentration ((Ca2+_i)), permitting the further strengthening of synapses given appropriate additional stimuli.

L2 ANSWER 6 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

ACCESSION NUMBER: 2002:307066 BIOSIS
DOCUMENT NUMBER: PREV200200307066
TITLE: Hyperpolarization-activated current Ih in nucleus of solitary tract neurons: Igegal difference in serotonergic modulation.

AUTHOR(S): Iwahori, Yuki; Ikegaya, Yuji (1); Matsuki, Norio
CORPORATE SOURCE: (1) Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo,

113-0033: ikegaya@tk.aimet.ne.jp Japan

SOURCE: Japanese Journal of Pharmacology, (April, 2002) Vol. 88,

No. 4, pp. 459-462. <http://www.pharmacol.or.jp>. print. ISSN: 0021-5198.

DOCUMENT TYPE: Article
LANGUAGE: English
AB The nucleus of solitary tract (NTS) contains diverse neural circuits responsible for basic vital functions. We examined the effect of

serotonin (5-HT) on hyperpolarization-activated current (Ih) in neurons acutely isolated from caudal, medial and rostral parts of the NTS. Caudal and medial NTS neurons showed a large amplitude of Ih compared with rostral neurons. In these neurons, perfusion with 5-HT potentiated Ih amplitude in a concentration-dependent manner. The effect of 5-HT was blocked by NAN-190, a 5-HT1A receptor antagonist. Thus, 5-HT1A receptors may regulate ***Ih*** ***channel*** activity in caudal and medial NTS neurons.

L2 ANSWER 7 OF 68 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2002052186 MEDLINE
DOCUMENT NUMBER: 21636767 PubMed ID: 11778053
TITLE: Mediation of hippocampal mossy fiber long-term potentiation by presynaptic ***Ih*** ***channels***.
AUTHOR: Mellor Jack; Nicoll Roger A; Schmitz Dietmar
CORPORATE SOURCE: Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94143, USA.
SOURCE: SCIENCE, (2002 Jan 4) 295 (5552) 143-7.
Journal code: 0404511. ISSN: 0036-8075.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020130
Entered Medline: 20020129

AB Hippocampal mossy fiber long-term potentiation (LTP) is expressed presynaptically, but the exact mechanisms remain unknown. Here, we demonstrate the involvement of the hyperpolarization-activated cation channel (Ih) in the expression of mossy fiber LTP. Established LTP was blocked and reversed by ***Ih*** ***channel*** antagonists. Whole-cell recording from granule cells revealed that repetitive stimulation causes a calcium- and Ih-dependent long-lasting depolarization mediated by protein kinase A. Depolarization at the terminals would be expected to enhance transmitter release, whereas somatic depolarization would enhance the responsiveness of granule cells to afferent input. Thus, ***Ih*** ***channels*** play an important role in the long-lasting control of transmitter release and neuronal excitability.

L2 ANSWER 8 OF 68 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2002416446 IN-PROCESS
DOCUMENT NUMBER: 22162713 PubMed ID: 12172637
TITLE: Modulation by PKA of the Hyperpolarization-activated Current (Ih) in Cultured Rat Olfactory Receptor Neurons.
AUTHOR: Vargas G; Lucero M T
CORPORATE SOURCE: Department of Physiology, University of Utah, School of Medicine, 410 Chipeta Way, Salt Lake City, UT 84108-1297, USA.
SOURCE: JOURNAL OF MEMBRANE BIOLOGY, (2002 Jul 15) 188 (2) 115-25.
Journal code: 0211301. ISSN: 0022-2631.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20020813

AB The hyperpolarization-activated ***Ih*** ***channel*** is modulated by neurotransmitters acting through the cAMP messenger system. In rat olfactory receptor neurons (ORNs), dopamine, by inhibition of adenylyl cyclase, shifts the voltage of half-maximal activation (V1/2) of Ih to more negative potentials and decreases Ih maximal relative conductance. Whether these effects result from a phosphorylation-dependent mechanism is unclear. Therefore, we used whole-cell patch-clamp recording techniques to study cAMP-dependent phosphorylation via PKA on Ih in ORNs. General protein kinase inhibition (50 nM K252a) produced a hyperpolarizing shift in Ih V1/2 and decreased Ih maximal conductance. Specific inhibition of PKA with H-89 (500 nM) also shifted the V1/2 of Ih to more negative potentials, and, in some cells, decreased Ih maximal conductance. PKA-mediated phosphorylation (cBIMPS, 50 mM) shifted Ih V1/2 more positive, modulated the kinetics of ***Ih*** ***channel*** activation and increased Ih peak current amplitude. Internal perfusion of the catalytic subunit of PKA (84 nM) also shifted Ih V1/2 positive and this shift was blocked by co-perfusion with PKI (50 nM). These results show that in rat ORNs, the voltage dependence of Ih activation can be modulated by PKA-dependent phosphorylation. We also show that PKA and other protein kinases may be involved in the regulation of Ih maximal conductance. Our findings suggest that changes in the phosphorylation state of ORNs may affect resting properties as well as modulate odor sensitivity.

L2 ANSWER 9 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:868487 CAPLUS
DOCUMENT NUMBER: 136:1740
TITLE: Full length human hyperpolarised activated ion channel and variants and therapeutic uses

INVENTOR(S): Morrow, John Anthony; Dunbar, Donald Robert; Tolan, Deborah Grace
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001090142	A2	20011129	WO 2001-EP5959	20010522

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GE, GR, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: EP 2000-304420 A 20000524 EP 2001-201344 A 20010412

AB This invention relates to a cDNA sequence encoding a member of the hyperpolarised activated ion channel family (HCN) and variants thereof, and the use of said sequences in assays for the measurement of gene expression. It also relates to assays for screening of Ih activators and blockers for clin. and therapeutic use in the management of human psychiatric and neurol. dysfunction in the CNS, cardiovascular dysfunction of the heart, and reproductive dysfunction and/or contraception related to Ih function in testes and spermatozoa. Further, antibodies against the expressed DNA sequences and other compds. reactive with the expressed DNA sequence are also part of the invention.

L2 ANSWER 10 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:3118 BIOSIS
DOCUMENT NUMBER: PREV20020003118
TITLE: Ih and IA channels shape the functional topography of dopaminergic midbrain neurons.
AUTHOR(S): Neuhoff, H. (1); Neu, A. (1); Liss, B. (1); Roeper, J. (1)
CORPORATE SOURCE: (1) Medical Research Council, Anatomical Neuropharmacology Unit, Oxford UK
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2198. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
AB Different subclasses of dopaminergic (DA) midbrain neurons show distinct functional properties and differential involvement in basal ganglia disorders. To investigate their topographical distribution, DA neurons in mouse midbrain slices were characterized using whole-cell patch-clamp recordings followed by immunocytochemical identification. The topographical positions of tyrosine hydroxylase immuno-positive neurons (>300) were plotted in a map representing the substantia nigra (SN) and the ventral tegmental area (VTA). Different DA subpopulations were identified based on their localization, immunoreactivity for calbindin (CB), and their distinct electrophysiological properties. In both SN and VTA, CB-positive DA neurons possessed significantly longer rebound delays after hyperpolarization compared to CB-negative DA neurons. These differences in rebound delays were strongly correlated with both differences in IA-channel and ***Ih*** - ***channel*** densities between distinct DA subpopulations. These results indicate that the ratio between IA and ***Ih*** ***channel*** densities is an important determinant for subthreshold behavior in DA neurons. Surprisingly, only in one of the four subpopulations ***Ih*** ***channels*** contribute to pacemaker frequency control, namely in the calbindin-negative SN neurons. By contrast the discharge frequencies of the other three DA subpopulations are not affected by selective Ih inhibition using 30umM ZD7288. This remarkable diversity of DA neurons might have important implications for the study of basal ganglia function and pathology of basal ganglia disorders.

L2 ANSWER 11 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:562807 BIOSIS
DOCUMENT NUMBER: PREV200100562807
TITLE: Development of spontaneous firing patterns in cerebellar Purkinje neurons.
AUTHOR(S): Hausser, M. (1); Jackson, A. (1); Miller, P. (1); Clark,

B. (1)
CORPORATE SOURCE: (1) Physiology, University College London, London UK
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1882. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Spontaneous firing plays an important role in the development of neuronal networks. In the mature cerebellar cortex, both Purkinje cells (PCs) and interneurons are spontaneously active in the absence of synaptic input, with interneuron inputs contributing to the irregular firing pattern of PCs. We investigated how spontaneous firing and the interactions between these neurons change during maturation. Cell-attached and extracellular recordings were made from PCs in sagittal slices prepared from P5-P20 rats and maintained at physiological temperatures (35+-1C). The mean firing frequency of PCs increased dramatically with age. At P5, only approx 50% of PCs showed spontaneous activity, and those that did fired at low rates (6.8+-2.3 Hz; n=22). Firing rates increased progressively during the second postnatal week, with virtually all P20 PCs exhibiting spontaneous firing at a mean rate of 52.4+-4.9 Hz (n=34). Recordings from nucleated outside-out patches revealed that the increase in spontaneous firing rate was associated with an increased density of voltage-gated sodium and ***Ih*** ***channels***. Interestingly, at P5 variability in firing was substantial (CV=0.40) and insensitive to block of synaptic inhibition by picrotoxin, while at P15-20 variability was lower (CV approx 0.15) and significantly reduced by picrotoxin. This indicates that intrinsic variability predominates in immature PCs, in contrast to mature PCs where variability is driven by inhibitory synaptic input. As the timecourse of these changes parallels the maturation of motor behaviour, this suggests that spontaneous firing and the irregularity produced by interneuron-PC connections may be important determinants of cerebellar function.

L2 ANSWER 12 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:562719 BIOSIS
DOCUMENT NUMBER: PREV200100562719
TITLE: Reciprocal modulation of TASK and Ih currents in rat hypoglossal motoneurons by neurotransmitters and anesthetics.
AUTHOR(S): Sirois, J. E. (1); Lynch, C., III; Bayliss, D. A. (1)
CORPORATE SOURCE: (1) Dept Pharmacol, Univ Virginia, Charlottesville, VA USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1861. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We examined interactions of halothane and neurotransmitters on TASK (K+) and hyperpolarization-activated (Ih) currents in rat hypoglossal motoneurons. Halothane enhanced neurotransmitter-induced currents (I5-HT and INE) by 55 and 51%. Halothane-enhanced neurotransmitter currents displayed I-V relationships with slight outward rectification, but did not reverse at EK, consistent with effects on additional conductances (e.g., Ih). When cells were recorded with ZD 7288 (40 umM) in the pipette to block Ih and isolate effects on TASK channels, I5-HT and INE were still enhanced by halothane, but the halothane-sensitive I5-HT and INE reversed at EK and were well fit with a constant field equation, indicating that they resulted entirely from inhibition of open-rectifying K+ channels (i.e., TASK). To characterize effects on Ih in relative isolation cells were recorded in acidified bath solutions (pH 6.0-6.5) to block TASK channels. Under these conditions, Ih activation was shifted to more hyperpolarized potentials with a corresponding decrease in current amplitude; from this new point, however, halothane remained capable of inducing a further hyperpolarizing shift and 5-HT of inducing its characteristic depolarizing shift in Ih activation. When tested concurrently in low pH conditions, halothane decreased the 5-HT-induced depolarizing shift in Ih activation and diminished I5-HT. Thus, halothane and neurotransmitters converge with opposite effects on TASK and ***Ih*** ***channels*** in motoneurons; transmitter action prevails over anesthetic effects on TASK channels but not over effects on Ih.

L2 ANSWER 13 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:548070 BIOSIS
DOCUMENT NUMBER: PREV200100548070
TITLE: Presynaptic ***Ih*** ***channels*** mediate hippocampal mossy fiber long term potentiation.

AUTHOR(S): Mellor, J. R. (1); Schmitz, D. (1); Nicoll, R. A. (1)
CORPORATE SOURCE: (1) Pharmacology, UCSF, San Francisco, CA
USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27,
No. 2,

pp. 1590. print.
Meeting Info.: 31st Annual Meeting of the Society for
Neuroscience San Diego, California, USA November 10-15,
2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hippocampal mossy fiber long term potentiation (LTP) is thought to
be

induced and expressed presynaptically. The induction pathway is
believed
to start with calcium influx activating a calcium-dependent adenylate
cyclase which increases cAMP within the presynaptic terminal. The
mechanism by which cAMP causes synaptic enhancement is unknown
but thought

to involve the proteins Rab3A and RIM. Here we demonstrate the
involvement
of hyperpolarization-activated cation channels (*****Ih*****
*****channels*****) in this pathway. Application of the specific
*****Ih*****

*****channel***** blocker ZD7288 (50 μ M) blocked LTP induction
when applied
before a tetanus and reversed. LTP when applied afterwards: Another
*****Ih***** *****channel***** blocker DK-AH269 (100 μ M) also
reversed LTP.

These results implicate *****Ih***** *****channels***** in the
maintenance
of mossy fiber LTP. Furthermore, forskolin induced enhancement of
mossy
fiber synaptic transmission was also blocked and reversed by ZD7288
thus

demonstrating that the two methods of synaptic enhancement share a
common

locus of expression. We also show that ZD7288 acts presynaptically to
depress baseline synaptic transmission. ZD7288 increased paired pulse
facilitation and depressed both AMPA and NMDA receptor-mediated
responses

equally. Therefore we conclude that *****Ih***** *****channels***** are
tonically active in the presynaptic terminal and contribute to the release
of synaptic vesicles. These *****Ih***** *****channels***** are then
upregulated in some fashion by tetanic stimulation or increased cAMP
and

cause an increase in synaptic release probability.

L2 ANSWER 14 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL
ABSTRACTS INC.

ACCESSION NUMBER: 2001:540663 BIOSIS
DOCUMENT NUMBER: PREV200100540663

TITLE: Cloning and expression of two splicing isoforms of the
human *****Ih***** *****channel***** subunit HCN1.

AUTHOR(S): Morrow, J. A. (1); Tolán, D. G. (1); Dunbar, D. R.
(1);

McShane, T. (1); Hill, D. R. (1); van Duin, M. (1); Mason,
A. (1)

CORPORATE SOURCE: (1) Research and Development, Organon Labs.
Ltd.,

Lanarkshire UK
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27,
No. 2,

pp. 1580. print.
Meeting Info.: 31st Annual Meeting of the Society for
Neuroscience San Diego, California, USA November 10-15,
2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Hyperpolarisation-activated cation channels that are directly regulated
by

cyclic nucleotides, known as *****Ih***** *****channels*****, mediate
the

generation of pacemaker activity in neuronal and cardiac tissue. In the
CNS, *****Ih***** *****channels***** are involved in the control of
neuronal network synchronisation, modulation of sleep-wake cycles and
in

the retina, counteract hyperpolarising light stimuli. Four separate genes
encoding mammalian *****Ih***** *****channels*****, known as HCN
1-4, have

been identified and demonstrated to be expressed in the brain. We have
now

cloned two splicing isoforms of the human HCN1 subunit which differ
by a

single 189bp exon in the region encoding the predicted C-terminal
domain

of the channel. These human HCN1 sequences are highly homologous
to the

murine HCN1 sequence sharing over 90% homology at the amino acid
level.

Whole-cell patch-clamp recordings were made from HEK cells
transfected
with either isoform. From a holding potential of -40 mV,
hyperpolarising
steps evoked slowly developing inward currents whose amplitude and
rate of

activation increased with increasing hyperpolarisation. These currents
were reduced by caesium ions and by the specific *****Ih*****
*****channel***** blocker, ZD 7288. In view of recent results
implicating Ih

as a mechanistic component of an animal model of epilepsy, the future
development of subtype selective *****Ih***** *****channel***** ligands
may prove effective tools for the treatment of epilepsy as well as other
CNS disorders.

L2 ANSWER 15 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL
ABSTRACTS INC.

ACCESSION NUMBER: 2001:540664 BIOSIS
DOCUMENT NUMBER: PREV200100540664

TITLE: Modulation of AtT20 D16:16 mixed cation
hyperpolarisation-activated current by intracellular pH.

AUTHOR(S): Southan, A. P. (1); Elsegood, K. A. (1); Garrett, S. A.
(1); Speight, G. J. (1)

CORPORATE SOURCE: (1) Channelwork, CeNes Ltd, Cambridge UK
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27,
No. 2,

pp. 1580. print.
Meeting Info.: 31st Annual Meeting of the Society for
Neuroscience San Diego, California, USA November 10-15,
2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Intracellular pH has been shown to modulate activation of
hyperpolarisation-activated mixed cation currents in both
thalamocortical

neurons (Munsch and Pape, 1999, J. Physiol., 519:2) and
heterologously

expressed HCN2 channels (Zong et al., J. Biol. Chem., 2001, 276:9).
Recently mouse anterior pituitary AtT20 D16:16 corticotropes have
been

shown to express a hyperpolarisation-activated cyclic-nucleotide
sensitive

mixed cation current which may be carried by HCN1 channel subunits
(Tian

and Shipston, 2000, Endocrinology, 141:8). Here we have used
whole-cell

patch-clamp techniques to further examine the electrophysiological
properties of the AtT20 D16:16 current and its sensitivity to
intracellular pH (pHi). In a bathing solution containing 35mM external
potassium D16:16 corticotropes exhibited a cesium-sensitive (IC50

27uM)
hyperpolarisation-activated current with PNa/PK value of 0.28 (pHi

7.3).
Recordings were made with predefined pipette solution pH values to

test
the pHi dependence of the AtT20 corticotrope Ih current (pipette pH

being
set with N-methyl-D-glucamine to keep the transmembrane driving

force for
potassium constant). With pipette solution set to the control value of

pH
7.3 current activation was well described by a Boltzmann function with
V1/2 -96mV (n=7). Acidic pipette pH (6.2) shifted V1/2 slightly

leftward
to -100mV (n=6), whilst alkaline pH (9.0) shifted the V1/2 by almost

30mV
to -69mV (n=7). Slope factor was 8mV for all pipette pH values. Our

results provide further evidence for modulation of *****Ih*****
*****channel***** activity by intracellular pH. Such modulation may

contribute towards the control of membrane potential and pacemaker
activity in a variety of cell types.

L2 ANSWER 16 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL
ABSTRACTS INC.

ACCESSION NUMBER: 2001:548033 BIOSIS
DOCUMENT NUMBER: PREV200100548033

TITLE: Ih shapes EPSPs of hippocampal interneurons.

AUTHOR(S): Hubbard, A. (1); Jaffe, D. B. (1)
CORPORATE SOURCE: (1) Div. of Life Sci., Cajal Neuroscience
Research Center,

Univ. of Texas at San Antonio, San Antonio, TX USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27,
No. 2,

pp. 1579. print.
Meeting Info.: 31st Annual Meeting of the Society for
Neuroscience San Diego, California, USA November 10-15,
2001

ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We investigated the role of the hyperpolarization activated current
(Ih)

on shaping EPSPs of rat hippocampal interneurons. Whole-cell
recordings

were made from CA1 and CA3 stratum radiatum interneurons in vitro
to test

the hypotheses that 1) Ih influences the shape of postsynaptic potentials
and 2) *****Ih***** *****channel***** density is differentially

distributed between dendrites and soma. As expected, inward
rectification

at hyperpolarized potentials was abolished by 50 μ M ZD7288 or 3
mM CsCl.

At potentials near rest, input resistance was unaffected by blocking Ih.
However, the amplitudes of simulated EPSP trains (5-20 pulses, 33-100

Hz)
generated by alpha function current injection to the soma were

increased
by blocking Ih (n=24). This effect was occluded when cells were held

10 mV
above rest, consistent with Ih deactivation (n=4). We next examined the

effect of blocking Ih on putative monosynaptic (single exponential

EPSC
decay time constant) commissural/associational or Schaffer collateral
EPSPs. In 2 of 5 cells, blocking Ih significantly increased the amplitude
and duration of EPSPs stimulated at low-frequency, while the amplitude
of

corresponding EPSCs remained the same or decreased. In contrast,
blocking

Ih had significantly less effect on somatically-generated simulated
EPSPs

suggesting Ih exerted greater control over distal synaptic events
compared

to somatically-generated signals. These preliminary results demonstrate
that Ih deactivation participates in shaping EPSPs in hippocampal

interneurons and *****Ih***** *****channels***** may be differentially
distributed between their soma and dendrites, as reported for pyramidal
cells in cortex and hippocampus.

L2 ANSWER 17 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL
ABSTRACTS INC.

ACCESSION NUMBER: 2001:532910 BIOSIS
DOCUMENT NUMBER: PREV200100532910

TITLE: beta-Adrenergic modulation of GABA release at
cerebellar

basket cell-Purkinje cell synapses.

AUTHOR(S): Saitow, F. (1); Ikebuchi, Y. (1); Konishi, S. (1)
CORPORATE SOURCE: (1) CREST JST, Mitsubishi Kasei Inst Life
Sci, Tokyo Japan

SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27,
No. 1,

pp. 1306. print.
Meeting Info.: 31st Annual Meeting of the Society for
Neuroscience San Diego, California, USA November 10-15,
2001

ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Our previous studies showed that beta2-adrenergic receptor
activation in

basket cells (BCs) increased BC spike discharges, thereby increasing in
the frequency of spike-triggered inhibitory postsynaptic currents

(IPSCs)

in Purkinje cells (PCs). Evidence was provided that the increase in BC
spike firing results from enhancement of hyperpolarization-activated

cation channels (Ih) by direct action of cAMP formed following
beta-adrenergic receptor (beta-AR) activation in BCs. In this study we

explored the beta2-adrenoceptor mediated enhancement of GABA
release at

BC-PC synapses. A beta-adrenoceptor agonist, isoproterenol (ISP),
enhanced

stimulation-evoked inhibitory postsynaptic currents (IPSCs) even after
*****Ih***** *****channel***** inhibition by ZD7288. The ISP-induced

enhancement of evoked IPSCs was attenuated by a protein kinase A
(PKA)

inhibitor, H-89. ISP increased the frequency of miniature IPSCs without
affecting their amplitude, and this effect was also inhibited by H-89.

GABAergic synaptic current induced by hypertonic sucrose solution
(HS) was

enhanced by ISP. There was strong correlation between the increase in
HS-induced currents and the frequency increase of mIPSCs induced by

ISP

application. Ca2+ transients in BC nerve terminals determined by a fast
scan imaging was not affected by ISP. Our data suggest that the size of

readily releasable pool (RRP) and release probability are co-regulated
by

beta-adrenoceptor activation in a PKA-dependent manner and that
Ca2+

influx into BC terminals does not contributed to the beta-AR-mediated
enhancement.

L2 ANSWER 18 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL
ABSTRACTS INC.

ACCESSION NUMBER: 2001:307861 BIOSIS
DOCUMENT NUMBER: PREV200100307861

TITLE: High *****Ih***** *****channel***** density in the distal
apical dendrite of layer V pyramidal cells increases

bidirectional attenuation of EPSPs.

AUTHOR(S): Berger, Thomas (1); Larkum, Matthew E.; Luscher,
Hans-R.

CORPORATE SOURCE: (1) Institute of Physiology, University of Bern,
Bühlplatz

5, CH-3012, Bern: berger@ppl.unibe.ch Switzerland
SOURCE: Journal of Neurophysiology (Bethesda), (February,
2001)

Vol. 85, No. 2, pp. 855-868. print.
ISSN: 0022-3077.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Despite the wealth of recent research on active signal propagation
along

the dendrites of layer V neocortical pyramidal neurons, there is still
little known regarding the traffic of subthreshold synaptic signals. We

present a study using three simultaneous whole cell recordings on the
apical dendrites of these cells in acute rat brain slices to examine the

spread and attenuation of spontaneous excitatory postsynaptic
potentials

(sEPSPs). Equal current injections at each of a pair of sites separated by
approx 500 μ m on the apical dendrite resulted in equal voltage

transients
at the other site ("reciprocity"), thus disclosing linear behavior of the
neuron. The mean apparent "length constants" of the apical dendrite

were
273 and 446 μ m for somatopetal and somatofugal sEPSPs,

respectively.

Trains of artificial EPSPs did not show temporal summation. Blockade of the hyperpolarization-activated cation current (I_h) resulted in less attenuation by 17% for somatopetal and by 47% for somatofugal sEPSPs. A pronounced location-dependent temporal summation of EPSP trains was seen.

The subcellular distribution and biophysical properties of I_h were studied in cell-attached patches. Within less than approx 400 μm of the soma, a low density of approx 3 pA/μm² was found, which increased to approx 40 pA/μm² in the apical distal dendrite. I_h showed activation and deactivation kinetics with time constants faster than 40 ms and half-maximal activation at -95 mV. These findings suggest that integration of synaptic input to the apical tuft and the basal dendrites occurs spatially independently. This is due to a high ***I_h*** ***channel*** density in the apical tuft that increases the electrotonic distance between these two compartments in comparison to a passive dendrite.

L2 ANSWER 19 OF 68 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2001410304 MEDLINE
DOCUMENT NUMBER: 21229737 PubMed ID: 11331358
TITLE: Properties of hyperpolarization-activated pacemaker current

defined by coassembly of HCN1 and HCN2 subunits and basal modulation by cyclic nucleotide.

AUTHOR: Chen S; Wang J; Siegelbaum S A
CORPORATE SOURCE: Department of Pharmacology, Columbia University, New York, New York 10032, USA.

CONTRACT NUMBER: RO1 NS-36658 (NINDS)
SOURCE: JOURNAL OF GENERAL PHYSIOLOGY, (2001 May) 117 (5) 491-504.

Journal code: 2985110R. ISSN: 0022-1295.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Members of the HCN channel family generate hyperpolarization-activated cation currents (I_h) that are directly regulated by cAMP and contribute to pacemaker activity in heart and brain. The four HCN isoforms show distinct but overlapping patterns of expression in different tissues. Here, we report that HCN1 and HCN2, isoforms coexpressed in neocortex and hippocampus that differ markedly in their biophysical properties, coassemble to generate heteromultimeric channels with novel properties.

When expressed in *Xenopus* oocytes, HCN1 channels activate 5-10-fold more rapidly than HCN2 channels. HCN1 channels also activate at voltages that

are 10-20 mV more positive than those required to activate HCN2. In cell-free patches, the steady-state activation curve of HCN1 channels shows a minimal shift in response to cAMP (+4 mV), whereas that of HCN2

channels shows a pronounced shift (+17 mV). Coexpression of HCN1 and HCN2

yields I_h currents that activate with kinetics and a voltage dependence that tend to be intermediate between those of HCN1 and HCN2

homomers, although the coexpressed channels do show a relatively large shift by cAMP

(+14 mV). Neither the kinetics, steady-state voltage dependence, nor cAMP

dose-response curve for the coexpressed I_h can be reproduced by the linear

sum of independent populations of HCN1 and HCN2 homomers. These results

are most simply explained by the formation of heteromeric channels with

novel properties. The properties of these heteromeric channels closely resemble the properties of I_h in hippocampal CA1 pyramidal neurons, cells that coexpress HCN1 and HCN2. Finally, differences in ***I_h***

channel properties recorded in cell-free patches versus intact oocytes are shown to be due, in part, to modulation of I_h by basal levels of cAMP in intact cells.

channel properties recorded in cell-free patches versus intact oocytes are shown to be due, in part, to modulation of I_h by basal levels of cAMP in intact cells.

channel properties recorded in cell-free patches versus intact oocytes are shown to be due, in part, to modulation of I_h by basal levels of cAMP in intact cells.

channel properties recorded in cell-free patches versus intact oocytes are shown to be due, in part, to modulation of I_h by basal levels of cAMP in intact cells.

L2 ANSWER 20 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9

ACCESSION NUMBER: 2001:421089 BIOSIS

DOCUMENT NUMBER: PREV200100421089

TITLE: Niflumic acid reduces the hyperpolarization-activated current (I_h) in rod photoreceptor cells.

AUTHOR(S): Satoh, Tomo-Okii; Yamada, Masahiro (1)

CORPORATE SOURCE: (1) Department of Production, Information and Systems Engineering, Tokyo Metropolitan Institute of Technology, 6-6, Asahigaoka, Hino, Tokyo, 191-0065;

myamada@cc.tmit.ac.jp Japan

SOURCE: Neuroscience Research, (August, 2001) Vol. 40, No. 4, pp.

375-381. print.

ISSN: 0168-0102.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We examined the effects of niflumic acid (NFA), a chloride channel blocker, on the hyperpolarization-activated current (I_h) in new rod photoreceptors. At 100 μM, NFA delayed the activation of I_h induced

by hyperpolarizing voltage pulses to -83 mV from a holding potential of -43

mV, and reduced the steady-state current. However, reduction by NFA

was weakened when I_h was activated by hyperpolarizing steps to -123 mV,

suggesting that these effects were voltage-dependent. The suppressive effects of NFA on I_h were accompanied by a negative shift in activation

voltage. NFA also delayed the relaxation of I_h tail currents, showing

that this drug also inhibited deactivation of the current. The reversal potential and the fully activated conductance were not affected. These

observations suggest that NFA reduces I_h by modifying the gating kinetics

of the underlying channels. The suppressive actions of NFA remained when

intracellular Ca²⁺ was strongly chelated, and the failure of suppression by NFA in inside-out patches suggests that the agent may act on the

I_h ***channel*** from the extracellular side. These results,

obtained in rod photoreceptors, are consistent with similar effects of NFA

on I_f in cardiac myocytes, suggesting that both currents share similar pharmacological properties.

L2 ANSWER 21 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10

ACCESSION NUMBER: 2001:139718 BIOSIS

DOCUMENT NUMBER: PREV200100139718

TITLE: Molecular mechanism for ZD7288 block of hyperpolarization-activated cation (***I_h***)

channels .

AUTHOR(S): Shin, Ki Soon (1); Rothberg, Brad (1); Yellen, Gary (1)

CORPORATE SOURCE: (1) Harvard Medical School, Boston, MA, 02115 USA

SOURCE: Biophysical Journal, (January, 2001) Vol. 80, No. 1 Part 2,

pp. 337a. print.

Meeting Info.: 45th Annual Meeting of the Biophysical Society Boston, Massachusetts, USA February 17-21, 2001

Biophysical Society . ISSN: 0006-3495.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L2 ANSWER 22 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11

ACCESSION NUMBER: 2001:509745 BIOSIS

DOCUMENT NUMBER: PREV200100509745

TITLE: Propofol suppresses a hyperpolarization-activated inward current in rat hippocampal CA1 neurons.

AUTHOR(S): Funahashi, Makoto (1); Higuchi, Hitoshi; Miyawaki, Takuya;

Shimada, Masahiko; Matsuo, Ryuji

CORPORATE SOURCE: (1) Department of Oral Physiology, Okayama University

Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Okayama, 700-8525;

mfuna@md.okayama-u.ac.jp Japan

SOURCE: Neuroscience Letters, (October 5, 2001) Vol. 311, No. 3,

pp. 177-180. print.

ISSN: 0304-3940.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We examined the effect of propofol and thiopental, intravenous anesthetics, on the hyperpolarization-activated inward current (I_h), whose

functional role on the neuronal activity has been evaluated. Whole-cell recordings of I_h evoked by hyperpolarizing step pulses were taken from hippocampal CA1 neurons in rat brain slices. Propofol reduced I_h

current in a dose-dependent manner. However, thiopental had no significant effect

on the activation of I_h. According to the functional role of I_h, the suppression of I_h should result in a reduction of neuronal activity. We

suggest that the effectiveness of propofol as an anticonvulsant or an antiemetic is associated with the blockade of the ***I_h***

channel .

L2 ANSWER 23 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 12

ACCESSION NUMBER: 2001:319360 BIOSIS

DOCUMENT NUMBER: PREV200100319360

TITLE: Molecular mechanism underlying facilitation of cerebellar GABA-mediated transmission following activation of monoaminergic afferent fibers.

AUTHOR(S): Konishi, S. (1); Saitow, F. (1); Satake, S. (1); Yamada, J.

(1); Ikebuchi, Y. (1); Suzuki, H. (1)

CORPORATE SOURCE: (1) Molecular Neurobiology Laboratory, Mitsubishi Kasei

Institute of Life Sciences and CREST, JST (Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation), 11 Minamiooya, Machida-shi,

Tokyo,

194-8511 Japan

SOURCE: Biogenic Amines, (2001) Vol. 16, No. 2, pp. 115-125. print.

ISSN: 0168-8561.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Noradrenaline (NA) and serotonin (5-HT) released by electrical stimulation

into the rat cerebellar cortex from afferent input terminals have been shown to elicit long-term facilitation of inhibitory GABAergic

transmission between interneurons, basket cells (BCs), and Purkinje cells

(PCs). This study aimed to further examine receptor mechanisms underlying

the noradrenergic facilitation. Using cerebellar slices cut from neonatal rats and patch-clamp recordings, we explored the actions of

adrenoceptor agonists and antagonists on GABAergic synapses. GABA-mediated inhibitory

postsynaptic currents (IPSCs) were evoked by focal stimulation and recorded from PCs. Application of NA or isoproterenol (ISP), a

beta-receptor agonist, increased the amplitude of IPSCs and the frequency

of miniature IPSCs without affecting postsynaptic GABA receptor sensitivity and mean amplitude of miniature IPSCs. The enhancement by

NA of IPSCs was suppressed by a beta2-adrenoceptor antagonist, IC118,551,

but not by a beta1-adrenoceptor antagonist, CGP20712A, suggesting that the

beta2-adrenoceptors on BCs mediate the noradrenergic facilitation of GABAergic transmission. Then we performed double recordings from

BCs and PCs, which showed that the beta-agonist ISP increased the frequencies of

the spontaneous spikes in BCs and the spike-triggered IPSCs in PCs. Forskolin mimicked the actions of beta-agonist in enhancing BC spiking

and spike-triggered IPSCs in PCs. Furthermore, voltage-clamp experiments showed that BCs exhibit profound activity of a

hyperpolarization-activated cation channel current, I_h, and that ISP and forskolin enhanced

persistent activation of ***I_h*** ***channel*** . NA and ISP induced BC depolarization, which was abolished by the I_h inhibitor ZD7288. Taken

together, our data suggest that beta-adrenoceptor-mediated acceleration of

I_h in BCs is involved, at least in part, in noradrenergic facilitation of GABAergic transmission at BC-PC inhibitory synapses.

L2 ANSWER 24 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 13

ACCESSION NUMBER: 2001:120119 BIOSIS

DOCUMENT NUMBER: PREV200100120119

TITLE: Blocker state dependence and trapping in hyperpolarization-activated cation channels: Evidence for an intracellular activation gate.

AUTHOR(S): Shin, Ki Soon; Rothberg, Brad S.; Yellen, Gary (1)

CORPORATE SOURCE: (1) Department of Neurobiology, Harvard Medical School, 220

Longwood Avenue, Boston, MA, 02115;

gary_yellen@hms.harvard.edu USA

SOURCE: Journal of General Physiology, (February, 2001) Vol. 117,

No. 2, pp. 91-101. print.

ISSN: 0022-1295.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hyperpolarization-activated cation currents (I_h) are key determinants of

repetitive electrical activity in heart and nerve cells. The bradycardic agent ZD7288 is a selective blocker of these currents. We studied the

mechanism for ZD7288 blockade of cloned ***I_h***

channels in excised inside-out patches. ZD7288 blockade of the mammalian mHCN1 channel

appeared to require opening of the channel, but strong hyperpolarization

disfavored blockade. The steepness of this voltage-dependent effect (an

apparent valence of approx 4) makes it unlikely to arise solely from a direct effect of voltage on blocker binding. Instead, it probably

indicates a differential affinity of the blocker for different channel conformations. Similar properties were seen for ZD7288 blockade of

the sea urchin homologue of ***I_h*** ***channels*** (SPIH), but some of

the blockade was irreversible. To explore the molecular basis for the difference in reversibility, we constructed chimeric channels from

mHCN1 and SPIH and localized the structural determinant for the reversibility to three residues in the S6 region likely to line the pore. Using a triple point mutant in S6, we also revealed the trapping of ZD7288 by the

closing of the channel. Overall, the observations led us to hypothesize that the residues responsible for ZD7288 block of ***I_h***

channels
are located in the pore lining, and are guarded by an intracellular activation gate of the channel.

L2 ANSWER 25 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:156368 BIOSIS
DOCUMENT NUMBER: PREV200200156368
TITLE: Could ***Ih*** ***channels*** contribute to the seizure generation in the rabbit hippocampus.
AUTHOR(S): Kitayama, Masaomi (1); Kogure, Shinichi (1); Miyata, Harue (1); Saito, Nobuko (1); Yano, Michiko (1); Matsuda, Yoshiaki; Yamauchi, Toshio
CORPORATE SOURCE: (1) Bioengineering, Soka Univ., Hachioji Japan
SOURCE: Epilepsia, (2001) Vol. 42, No. Supplement 7, pp. 81-82.
http://www.blackwell-science.com/cglib/binc-bin?Journal=epilepsia.print.
Meeting Info.: Annual Meeting of the American Epilepsy Society Philadelphia, PA, USA November 30-December 05, 2001
ISSN: 0013-9580.
DOCUMENT TYPE: Conference
LANGUAGE: English

L2 ANSWER 26 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:356954 BIOSIS
DOCUMENT NUMBER: PREV200100356954
TITLE: Molecular biological and electrophysiological characterization of ***Ih*** ***channels*** in olfactory receptor neurons of Perca fluviatilis.
AUTHOR(S): Alberti, S. M. (1); Gamerschlag, B. (1); Gisselmann, G. (1); Wetzel, C. H. (1); Hatt, H. (1)
CORPORATE SOURCE: (1) Lehrstuhl fuer Zellphysiologie, Ruhr-Universitaet Bochum, Universitaetsstrasse 150, 44780, Bochum Germany
SOURCE: Zoology (Jena), (2001) Vol. 103, No. Supplement 3, pp. 62.
print.
Meeting Info.: 93rd Annual Meeting of the Deutsche Zoologische Gesellschaft Bonn, Germany June 12-16, 2000
ISSN: 0944-2006.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 27 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:663307 CAPLUS
DOCUMENT NUMBER: 136:81348
TITLE: Evolution of potassium channel proteins
AUTHOR(S): Gallin, Warren J.; Spencer, Andrew N.
CORPORATE SOURCE: Department of Biological Sciences, University of Alberta, Edmonton, AB, T6G 2E9, Can.
SOURCE: Potassium Channels in Cardiovascular Biology (2001), 3-16. Editor(s): Archer, Stephen L.; Rusch, Nancy J. Kluwer Academic/Plenum Publishers: New York, N. Y. CODEN: 69BUE4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review is given on the origin of major K⁺ channel families. The evolution of inward rectifier channels (Kir family), voltage-gated channels (Kv family), EAG family channels, and hyperpolarization-activated (***Ih***) ***channels*** is described.
REFERENCE COUNT: 27 THERE ARE 27 CITED
REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 28 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
ACCESSION NUMBER: 2000:353666 BIOSIS
DOCUMENT NUMBER: PREV200000353666
TITLE: Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS.
AUTHOR(S): Santoro, Bina (1); Chen, Shan; Luthi, Anita; Pavlidis, Paul; Shumyatsky, Gleb P.; Tibbs, Gareth R.; Siegelbaum, Steven A.
CORPORATE SOURCE: (1) Center for Neurobiology and Behavior, 722 West 168th Street, New York, NY, 10032 USA
SOURCE: Journal of Neuroscience, (July 15, 2000) Vol. 20, No. 14, pp. 5264-5275. print.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The hyperpolarization-activated cation current (termed Ih, Iq, or If) was recently shown to be encoded by a new family of genes, named HCN for hyperpolarization-activated cyclic nucleotide-sensitive cation nonselective. When expressed in heterologous cells, each HCN isoform generates channels with distinct activation kinetics, mirroring the range of biophysical properties of native Ih currents recorded in different classes of neurons. To determine whether the functional diversity of Ih

currents is attributable to different patterns of HCN gene expression, we determined the mRNA distribution across different regions of the mouse CNS of the three mouse HCN genes that are prominently expressed there (mHCN1, 2 and 4). We observed distinct patterns of distribution for each of the three genes. Whereas mHCN2 shows a widespread expression throughout the CNS, the expression of mHCN1 and mHCN4 is more limited, and generally complementary. mHCN1 is primarily expressed within neurons of the neocortex, hippocampus, and cerebellar cortex, but also in selected nuclei of the brainstem. mHCN4 is most highly expressed within neurons of the medial habenula, thalamus, and olfactory bulb, but also in distinct neuronal populations of the basal ganglia. Based on a comparison of mRNA expression with an electrophysiological characterization of native Ih currents in hippocampal and thalamic neurons, our data support the idea that the functional heterogeneity of ***Ih*** ***channels*** is attributable, in part, to differential isoform expression. Moreover, in some neurons, specific functional roles can be proposed for ***Ih*** ***channels*** with defined subunit composition.

L2 ANSWER 29 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:272104 BIOSIS
DOCUMENT NUMBER: PREV200000272104
TITLE: Site independence of EPSP time course is mediated by dendritic Ih in neocortical pyramidal neurons.
AUTHOR(S): Williams, Stephen R.; Stuart, Greg J. (1)
CORPORATE SOURCE: (1) Division of Neuroscience, John Curtin School of Medical Research, Australian National University, Mills Rd., Canberra, ACT, 0200 Australia
SOURCE: Journal of Neurophysiology (Bethesda), (May, 2000) Vol. 83, No. 5, pp. 3177-3182. print.
ISSN: 0022-3077.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Neocortical layer 5 pyramidal neurons possess long apical dendrites that receive a significant portion of the neurons excitatory synaptic input. Passive neuronal models indicate that the time course of excitatory postsynaptic potentials (EPSPs) generated in the apical dendrite will be prolonged as they propagate toward the soma. EPSP propagation may, however, be influenced by the recruitment of dendritic voltage-activated channels. Here we investigate the properties and distribution of ***Ih*** ***channels*** in the axon, soma, and apical dendrites of neocortical layer 5 pyramidal neurons, and their effect on EPSP time course. We find a linear increase (9 pA/100 μm) in the density of dendritic ***Ih*** ***channels*** with distance from soma. This nonuniform distribution of ***Ih*** ***channels*** generates site independence of EPSP time course, such that the half-width at the soma of distally generated EPSPs (up to 435 μm from soma) was similar to somatically generated EPSPs. As a corollary, a normalization of temporal summation of EPSPs was observed. The site independence of somatic EPSP time course was found to collapse after pharmacological blockade of ***Ih*** ***channels***, revealing pronounced temporal summation of distally generated EPSPs, which could be further enhanced by TTX-sensitive sodium channels. These data indicate that an increasing density of apical dendritic ***Ih*** ***channels*** mitigates the influence of cable filtering on somatic EPSP time course and temporal summation in neocortical layer 5 pyramidal neurons.

L2 ANSWER 30 OF 68 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 2000493221 MEDLINE
DOCUMENT NUMBER: 20428252 PubMed ID: 10971612
TITLE: Single-cell mRNA expression of HCN1 correlates with a fast gating phenotype of hyperpolarization-activated cyclic nucleotide-gated ion channels (Ih) in central neurons.
AUTHOR: Franz O; Liss B; Neu A; Roeper J
CORPORATE SOURCE: Medical Research Council, Anatomical Neuropharmacology Unit, Department of Pharmacology, Oxford University, UK.
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2000 Aug) 12 (8) 2685-93.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019
AB Hyperpolarization-activated currents (Ih) are key players in shaping rhythmic neuronal activity. Although candidate genes for ***Ih*** ***channels*** have been cloned (HCN1-HCN4), the subunit composition of different native ***Ih*** ***channels*** is unknown. We used a

combined patch-clamp and qualitative single-cell reverse transcription multiplex polymerase chain reaction (RT-mPCR) approach to analyse HCN1-4 coexpression profiles in four neuronal populations in mouse CNS. Coexpression of HCN2, HCN3 and HCN4 mRNA was detected in single neurons of all four neuronal cell types analysed. In contrast, HCN1 mRNA was detected in neocortical and hippocampal pyramidal neurons but not in dopaminergic midbrain and thalamocortical neurons. HCN1 expression was correlated with significantly faster activation kinetics on the level of individual neurons. Semiquantitative single-cell RT-mPCR analysis demonstrated that HCN1 mRNA expression is at least eightfold higher in cortical neurons than subcortical neurons. We show that single neurons possess complex coexpression patterns of Ih candidate genes. Alternative expression of HCN1 is likely to be an important molecular determinant to generate the different neuronal ***Ih*** ***channel*** species adapted to tune either subcortical or cortical network activity.

L2 ANSWER 31 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16
ACCESSION NUMBER: 2000:248769 BIOSIS
DOCUMENT NUMBER: PREV200000248769
TITLE: A bradycardiac agent ZD7288 blocks the hyperpolarization-activated current (Ih) in retinal rod photoreceptors.
AUTHOR(S): Satoh, Tomo-Oki; Yamada, Masahiro (1)
CORPORATE SOURCE: (1) Supermolecular Division, Electrotechnical Laboratory, Tsukuba, Ibaraki, 305-8568 Japan
SOURCE: Neuropharmacology, (April 27, 2000) Vol. 39, No. 7, pp. 1284-1291.
ISSN: 0028-3908.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recently it has been reported that "If channel blockers", which block the hyperpolarization-activated inward current (If) in heart sino atrial node cells, also block the hyperpolarization-activated inward current (Ih) in other tissues. Here we compared the effects of one of these agents, ZD7288 (4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride), with those of Cs⁺ on Ih in amphibian rod photoreceptors using patch clamp and intracellular recordings. ZD7288 strongly inhibited Ih in newt rod photoreceptors in a concentration-dependent manner (1-100 μM). ZD7288 exerted a blocking action on the conductance of Ih with no alteration of its gating properties, and the blocking action of Ih was not use-dependent. At concentrations as low as 1 μM, ZD7288 markedly enhanced the hyperpolarizing membrane responses of frog rod photoreceptors to bright light and delayed the response recovery, indicating that ZD7288 is highly selective for Ih. The apparent effect of the drug was slow in onset and irreversible, suggesting that ZD7288 act at a cytosolic site on the ***Ih*** ***channel***. These observations also confirm the involvement of Ih in accelerating the response recovery process from deep membrane hyperpolarization induced by bright light in rod cells.

L2 ANSWER 32 OF 68 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 2000177626 MEDLINE
DOCUMENT NUMBER: 20177626 PubMed ID: 10712631
TITLE: Hyperpolarization-activated current, Ih, in inspiratory brainstem neurons and its inhibition by hypoxia.
AUTHOR: Mironov S L; Langohr K; Richter D W
CORPORATE SOURCE: II Department of Physiology, University of Gottingen, Humboldtallee 23, Gottingen 37073, Germany.. sergej@neuro-physiol.med.uni-goettingen.de
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2000 Feb) 12 (2) 520-6.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000525
AB A hyperpolarization-activated current, Ih, is often implied in pacemaker-like depolarizations during rhythmic oscillatory activity. We describe Ih in the isolated respiratory centre of immature mice (P6-P11). Ih was recorded in 15% (22/146) of all inspiratory neurons examined. The mean half-maximal Ih activation occurred at -78 mV and the reversal potential was -40 mV. Ih was inhibited by Cs⁺ (1-5 mM) and by organic blockers N-ethyl-1,6-dihydro-1, 2-dimethyl-6-(methylimino)-N-phenyl-4-

pyrimidinamine (ZD 7288; 0.3-3 microM) and N,N'-bis-(3,4-dimethylphenylethyl)-N-methylamine (YS 035, 3-30 microM), but not by Ba2+ (0.5 mM). The organic lh blockers did not change the inspiratory bursts recorded from the XIIth nerve and synaptic drives in inspiratory neurons. Hypoxia reversibly inhibited lh but, in the presence of organic blockers, the hypoxic reaction remained unchanged. We conclude that although ***lh*** ***channels*** are functional in a minority of inspiratory neurons, lh does not contribute to respiratory rhythm generation or its modulation by hypoxia.

L2 ANSWER 33 OF 68 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 2000121710 MEDLINE
DOCUMENT NUMBER: 20121710 PubMed ID: 10658623
TITLE: Chronic morphine increases GABA tone on serotonergic neurons of the dorsal raphe nucleus: association with an up-regulation of the cyclic AMP pathway.
AUTHOR: Jolas T; Nestler E J; Aghajanian G K
CORPORATE SOURCE: Department of Psychiatry and Pharmacology, Yale University
School of Medicine and the Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven 06508, USA.
CONTRACT NUMBER: DA08227 (NIDA)
SOURCE: NEUROSCIENCE, (2000) 95 (2) 433-43.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229

AB Major adaptations after chronic exposure to morphine include an up-regulation of the adenosine 3',5'-monophosphate pathway. Acute opioids, via mu-opioid receptors, disinhibit midbrain serotonergic neurons by suppressing inhibitory GABAergic transmission in the dorsal raphe nucleus and adjacent periaqueductal gray. This study examined whether chronic morphine induces a compensatory increase in GABA inputs to 5-hydroxytryptamine neurons and whether this was associated with an up-regulation of the adenosine 3',5'-monophosphate pathway. The firing rate of serotonergic neurons was reduced in brain slices from morphine-dependent rats, an effect reversed by the GABA(A) antagonist bicuculline. The reduction in firing rate was accompanied by an increased frequency of spontaneous GABAergic inhibitory postsynaptic currents, indicating increased GABA tone in the slice. The increase in GABA tone in brain slices from dependent rats was associated with increased induction of inhibitory postsynaptic currents by the adenylyl cyclase activator forskolin, suggesting an up-regulation of the adenosine 3',5'-monophosphate pathway. Indeed, chronic morphine increased levels of adenylyl cyclase VIII (but not of adenylyl cyclase I, III or V) immunoreactivity in the dorsal raphe nucleus area. Two adenosine 3',5'-monophosphate-mediated mechanisms for the increase in GABA tone were discerned. The first, which predominated when impulse-flow was blocked by tetrodotoxin, involves protein kinase A since it was sensitive to protein kinase A inhibitors. The second, seen when impulse-flow was intact (i.e. absence of tetrodotoxin), was insensitive to protein kinase A inhibitors but was suppressed by ZD7288, a blocker of hyperpolarizing-activated ***lh*** ***channels*** which are directly activated by adenosine 3',5'-monophosphate. We conclude that chronic morphine induces an up-regulation of the adenosine 3',5'-monophosphate pathway in GABAergic inputs to serotonergic cells, resulting in an increase in spontaneous and impulse-flow dependent GABA release. These changes would lead to an increase in GABA tone and subsequently to the reported decrease in serotonergic activity during opiate withdrawal.

L2 ANSWER 34 OF 68 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 2000116101 MEDLINE
DOCUMENT NUMBER: 20116101 PubMed ID: 10649568
TITLE: Enhancement of synaptic transmission by cyclic AMP modulation of presynaptic ***lh*** ***channels***.
COMMENT: Comment in: Nat Neurosci. 2000 Feb;3(2):101-2
AUTHOR: Beaumont V; Zucker R S
CORPORATE SOURCE: Division of Neurobiology, Department of Molecular and Cell Biology, University of California, Berkeley, California 94720, USA. vahri@socrates.berkeley.edu
SOURCE: NATURE NEUROSCIENCE, (2000 Feb) 3 (2) 133-41.
Journal code: 9809671. ISSN: 1097-6256.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000407

AB Presynaptic activation of adenylyl cyclase and subsequent generation of cAMP represent an important mechanism in the modulation of synaptic transmission. In many cases, short- to medium-term modulation of

synaptic strength by cAMP is due to activation of protein kinase A and subsequent covalent modification of presynaptic ion channels or synaptic proteins. Here we show that presynaptic cAMP generation via serotonin receptor activation directly modulated hyperpolarization-activated cation channels (***lh*** ***channels***) in axons. This modulation of lh produced an increase in synaptic strength that could not be explained solely by depolarization of the presynaptic membrane. These studies identify a mechanism by which cAMP and lh regulate synaptic plasticity.

L2 ANSWER 35 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:221372 BIOSIS
DOCUMENT NUMBER: PREV20000221372
TITLE: Non-uniform distribution of Na+-influx through ***lh*** ***channels*** in the hippocampal CA1 pyramidal neurons.
AUTHOR(S): Tsubokawa, Hiroshi (1)
CORPORATE SOURCE: (1) Section of Brain Information, Center for Brain Experiment, NIPS, Okazaki, 444-8585 Japan
SOURCE: Japanese Journal of Pharmacology, (2000) Vol. 82, No. Suppl. 1, pp. 12P.
Meeting Info.: 73rd Annual Meeting of the Japanese Pharmacological Society, Yokohama, Japan March 23-25, 2000
ISSN: 0021-5198.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 36 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:108173 BIOSIS
DOCUMENT NUMBER: PREV200100108173
TITLE: Differential modulation of K+ currents by somatostatin receptors in rat thalamic neurons.
AUTHOR(S): Sun, Q. Q. (1); Parada, I.; Huguenard, J. R.; Prince, D. A.
CORPORATE SOURCE: (1) Stanford University, Stanford, CA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-530.14. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The physiological roles of somatostatin (SST) in thalamus are not clear.
Using patch clamp techniques applied to visualized neurons in thalamic slices from postnatal rats (P13-16), we studied the actions of SST on whole-cell currents. Focal application of SST activated a K+-selective current in neurons of the reticular nucleus (RT, 15/17 neurons), but inhibited K+ currents in ventral basal complex neurons (VB, 24/29). SST-sensitive currents in both nuclei showed inward rectification, were blocked by Ba2+ (0.1 mM), Cs+ (0.1 mM), and the GIRK channel inhibitor tertiapin-Q (10 nM) but not by the ***lh*** ***channel*** inhibitor ZD7288 (50 μM). These properties indicate that the SST-sensitive K+ current were mediated by GIRK channels. The activation of K+ currents in RT was mimicked by bim23052, while inhibition of K+ currents in VB was mimicked by NC4-28, suggesting that SST2 and SST5 receptors differentially couple to GIRK channels in RT and VB neurons, respectively. Addition of SST produced opposite effects on membrane properties in RT and VB neurons. It hyperpolarized RT neuron (approx 5 mV) and transformed firing mode from regular spiking to bursting, but it depolarized VB neurons (approx 4 mV) and reduced spike bursts. Recordings from VB dendrites (approx 60 μM from soma) revealed that SST-sensitive GIRK currents were approx 80% larger than those obtained from somatic recordings in the same neurons (n=7, p<0.01). Confocal microscopy with double-labeling revealed aggregations of SST-immunoreactive puncta, and dense somato-dendritic GIRK1 immunoreactivity. These data suggests the extrathalamic SST projections influence thalamic function via activation of multiple SST receptors in the somato-dendritic region.

L2 ANSWER 37 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:115013 BIOSIS
DOCUMENT NUMBER: PREV200100115013
TITLE: Interaction of a hyperpolarization-activated cation channel with the dynein light chain LC8.
AUTHOR(S): Jin, P. (1); Wen, H.; Levitan, I. B.
CORPORATE SOURCE: (1) University of Pennsylvania, Philadelphia, PA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-714.7. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000

1-2, pp. Abstract No.-714.7. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000

Society for Neuroscience
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The hyperpolarization-activated cation current (Ih) plays important roles in determining various neuronal membrane properties including input resistance, resting potential and oscillatory activity. The ion channels responsible for this current are encoded by the HCN gene family. To search for novel proteins that interact with ***lh*** ***channels***, we performed a yeast two-hybrid screen of a mouse brain cDNA library using the carboxyl terminal sequence of the cloned HCN1 channel as the bait. We found that the HCN1 channel interacts with the dynein light chain LC8 in the yeast two-hybrid assay. In addition, GST-LC8 fusion protein binds specifically to full-length HCN1 channel protein in a fusion protein pull-down assay, whereas the GST alone does not bind to the HCN1 channel. Truncation of the HCN1 carboxyl terminal sequence shows that the last 76 amino acids of the channel protein are still able to bind to LC8. When expressed in HEK293 cells, HCN1 gives rise to a typical hyperpolarization activated current with a V1/2 of about -80 mV. Co-expression of LC8 does not modulate channel activity. We are investigating the possible role of LC8 in other aspects of HCN1 channel function. Supported by a research grant from NIH.

L2 ANSWER 38 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:101606 BIOSIS
DOCUMENT NUMBER: PREV200100101606
TITLE: Long-term facilitation mediated by presynaptic ***lh*** ***channels***.
AUTHOR(S): Froemke, R. C. (1); Beaumont, V.; Zucker, R. S.
CORPORATE SOURCE: (1) Univ California, Berkeley, CA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-612.6. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Direct activation or cAMP-modulation of presynaptic ***lh*** ***channels*** enhances transmission at the crayfish NMJ (Beaumont & Zucker, 2000). We also found that ***lh*** ***channel*** activation mediates long-term facilitation (LTF), an enhanced synaptic strength lasting min. to hr. following a prolonged tetanus. Intracellular recording (2 Hz) of excitatory junction potentials (EJPs) showed an increase in EJP amplitude compared to pre-tetanic levels of 120 ± 27 % recorded between 30-60 min after a 20 Hz/10 min. tetanus (n = 9). The ***lh*** ***channel*** blocker ZD7288 (30 μM) reduced this enhancement to 33 ± 21% (n = 5, P<0.05). Recording of axon resting potential prior to and after the tetanus revealed that tetanic stimulation resulted in a transient (5-10 min) post-tetanic hyperpolarization of 1.2 ± 0.7 mV (n = 5), previously attributed to activation of the electrogenic Na+/K+ pump (Wojtowicz & Atwood, 1985). In ZD7288, this hyperpolarization was enhanced to 7.3 ± 3.2 mV and the time-course prolonged (n = 3), suggesting that normally ***lh*** ***channels*** become activated during a tetanus to maintain membrane potential. We propose that this activation of lh is responsible for LTF. cAMP has been implicated as the primary mediator of this enhancement (Dixon & Atwood, 1989). We have found no evidence to support a role for adenylyl cyclase and PKA activation in LTF. The adenylyl cyclase activator forskolin (30 μM) applied prior, during and after a tetanus did not occlude induction of LTF (n = 6, P>0.4). Furthermore, PKA inhibitors H-7 (30 μM) or Rp-S-Br cAMPs (300 μM) failed to reduce LTF (both n = 4, P>0.55). cAMP enhancement of transmission and LTF are attributed to an increase in quantal content (Wang & Zucker, 1998). Thus ***lh*** ***channel*** activation may alter vesicle pool size, perhaps by activation of a vesicle transport pathway. cAMP enhancement and LTF were reduced after treatment with actin depolymerizing agents cytochalasin D (10 μM) and latrunculin B (3 μM) (each n = 5, P<0.05). The role of an actin-dependent vesicle transport pathway under regulation in some way by ***lh*** ***channel*** activity is under further investigation.

L2 ANSWER 39 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:146426 BIOSIS
DOCUMENT NUMBER: PREV200100146426
TITLE: IH and temporal summation: a modeling study.
AUTHOR(S): Desjardins, A. E. (1); Li, Y. X.; Miura, R. M.;

Reinker, S.; Neuman, R. S.
CORPORATE SOURCE: (1) University of British Columbia, Vancouver, BC Canada
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-803.4. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
.ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recently, Magee (Nature Neuroscience 2, 508, 1999) reported that the magnitude of temporal summation in hippocampal CA1 neurons measured at the soma was equivalent whether the synaptic input arose from proximal or distal sites on the dendrite. This finding is contrary to expectations for a passive cable, in which temporal summation at the soma is larger for stimuli at distal sites. Magee, referring to this phenomenon as "spatial normalization of temporal integration", attributed the normalization to: 1) the voltage-dependent de-activation of IH (hyperpolarization activated cation current) by excitatory postsynaptic potentials, and; 2) the increased density of ***IH*** channels*** observed with increasing distance from the soma. We used computer simulations to study how IH influences the distorting effects of the dendritic arbor on temporal summation. Employing the stimulus protocol of Magee, we found that when IH was included (IH model based on Huguenard and McCormick, 1992), temporal summation was reduced, confirming the normalization. We are currently examining the sensitivity of this effect to the distribution of ***IH*** channels***.

L2 ANSWER 40 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:101591 BIOSIS
DOCUMENT NUMBER: PREV200100101591
TITLE: Co-localization of IH and IT channels in dendrites of thalamocortical neurons.
AUTHOR(S): Stuart, G. J. (1); Williams, S. R.
CORPORATE SOURCE: (1) JCSMR, ANU, Canberra ACT Australia
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-610.9. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
.ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Thalamocortical (TC) neurons generate oscillatory activity, formed by an interplay between the low-threshold calcium current (IT) and the hyperpolarisation-activated mixed cation current (IH). Calcium influx during low-threshold calcium potentials is capable of regulating the activation properties of IH and so the time-course of oscillatory activity. While IT channels have a predominant dendritic location, the somato-dendritic distribution of ***IH*** channels*** is unknown. Cell-attached recordings (n=42) at 35degC were obtained from the soma and dendrites of rat lateral geniculate TC neurons with pipettes (10-12MOMEGA) filled with a high K+ solution. In recordings from primary dendrites, from a holding potential 20mV positive to resting potential, negative voltage steps evoked ensemble inward channel activity that increased in amplitude and accelerated with potential negativity. The activation of this channel activity could be described with a single Boltzmann function with slope of -9.6 and half-maximal voltage of -82mV, and mono-exponential kinetics that accelerated from 0.88+-0.22s at -68 mV to 0.05+-0.01s at -138mV (n=6). In dendritic patches (n=37) we observed that following ***IH*** channels*** activity a transient inward current was generated at the offset of voltage command steps. The activation properties of this transient current were similar to those of IT, and this current was absent in recordings made with pipettes that contained 3mM Nickel (n=5). The amplitude of IH and IT channel activity were positively correlated. These data indicate that dendritic IH and IT channels are tightly co-localized, suggesting that in TC neurons dendritic calcium influx may serve to locally modulate ***IH*** channels***.

L2 ANSWER 41 OF 68 WPIDS (C) 2002 THOMSON DERWENT
DUPLICATE 20
ACCESSION NUMBER: 1999-527176 [44] WPIDS
DOC. NO. CPI: C1999-154784
TITLE: Use of new and known ***IH*** channels*** modulators for treating psychiatric disorders.
DERWENT CLASS: B05
INVENTOR(S): CARLYLE, I C; DUCKS, F A; GROVE, S J A; LEYSEN, D; LINDERS, J T M; RAE, D R; RUIGT, G S F; THORN, S N

PATENT ASSIGNEE(S): (ALKU) AKZO NOBEL NV; (CARL-I) CARLYLE I C; (DIJC-I) DUCKS F A; (GROV-I) GROVE S J A; (LEYS-I) LEYSEN D; (LIND-I) LINDERS J T M; (RAED-I) RAE D R; (RUIG-I) RUIGT
G S F; (THOR-I) THORN S N
COUNTRY COUNT: 74
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9918941	A2	19990422 (199944)*	EN	50	
RW:	AT BE CH CY DE DK EA ES FI FR GB GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG WZ W: AL AU BA BB BG BR CA CN CU CZ EE GE HU ID IL IS JP KR LR LC LK LR LT LV MG MK MN MX NO NZ PL RO RU SG SI SK SL TR TT UA US UZ VN YU AU 9922663 A 19990503 (199944) US 6080773 A 20000627 (200036) BR 9813047 A 20000815 (200045) EP 1035843 A2 20000920 (200047) EN R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE CN 1275909 A 20001206 (200118) US 6313139 B1 20011106 (200170) US 2002037885 A1 20020328 (200225)#				

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9918941	A2	WO 1998-EP6651	19981014
AU 9922663	A	AU 1999-22663	19981014
US 6080773	A	US 1997-950359	19971014
BR 9813047	A	BR 1998-13047	19981014
		WO 1998-EP6651	19981014
EP 1035843	A2	EP 1998-966232	19981014
		WO 1998-EP6651	19981014
CN 1275909	A	CN 1998-810196	19981014
US 6313139	B1 Div ex	US 1997-950359	19971014
		US 1999-359284	19990722
US 2002037885	A1 Div ex	US 1999-359284	19990722
		US 2001-933192	20010820

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9922663	A Based on	WO 9918941
BR 9813047	A Based on	WO 9918941
EP 1035843	A2 Based on	WO 9918941
US 6313139	B1 Div ex	US 6080773
US 2002037885	A1 Div ex	US 6313139

PRIORITY APPLN. INFO: US 1997-950359 19971014; US 1999-359284

19990722; US 2001-933192 20010820

AN 1999-527176 [44] WPIDS

AB WO 9918941 A UPAB: 19991026

NOVELTY - Use of new and known ***IH*** channels*** modulators

is claimed for treating psychiatric disorders.

DETAILED DESCRIPTION - Use of ***IH*** channels*** modulators is claimed for treating psychiatric disorders, provided that the modulator is not a compound of formula (D).

R1', R2' = 6-12C aryl, 2-14C heteroaryl, 6-12C aryl-(1-6C) alkyl or 2-14C heteroaryl-(1-6C) alkyl, (in which alkyl, aryl or heteroaryl are optionally substituted by one or more 1-6C alkoxy, 1-6C alkyl, 3-6C cycloalkyl, 4-6C cycloalkenyl, 6-12C aryl, 2-14C heteroaryl, halo, amino,

hydroxy, 1-6C haloalkyl, nitro, 1-6C alkylthio, sulfonamide, 1-6C alkylsulfonfyl, 1-6C hydroxyalkyl, 1-6C alkoxyalkyl, carboxyl, 1-6C carboxyalkyl, carboxamide or 1-6C alkylcarboxamide), H or 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl-(1-6C) alkyl, 4-6C cycloalkenyl, 2-6C alkyl, 2-6C alkynyl or 1-6C alkoxy-(1-6C) alkyl (all optionally substituted by one or more amino, halo, hydroxy, 1-6C alkylcarboxamide, carboxamide, carboxy, 1-6C alkoxyalkyl, 1-6C alkylcarboxyl or 1-6C carboxyalkyl) or

one of R1' and R2' is as defined above and the other is OH; R3', R4' = 6-12C aryl, 2-14C heteroaryl, 6-12C aryl-(1-6C) alkyl or 2-14C heteroaryl-(1-6C) alkyl, (all optionally substituted by one or more 1-6C alkoxy, 1-6C alkyl, 3-6C cycloalkyl, 4-6C cycloalkenyl, 6-12C aryl, 2-14C heteroaryl, halo, amino, hydroxy, 1-6C haloalkyl, nitro, 1-6C alkylthio, sulfonamide, 1-6C alkylsulfonfyl, 1-6C hydroxyalkyl, 1-6C alkoxyalkyl, 1-6C carboxyalkyl, carboxyl, 1-6C alkoxyalkyl, carboxamide or 1-6C alkylcarboxamide), H or 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl-(1-6C) alkyl, 4-6C cycloalkenyl, 2-6C alkyl, 2-6C alkynyl, 1-6C alkoxy-(1-6C) alkyl, 1-6C haloalkyl, 2-6C haloalkenyl, cyano, carboxyl, 1-6C alkylcarboxyl or 1-6C carboxyl-(1-6C)alkyl (all optionally substituted by one or more amino, hydroxy, 1-6C alkylcarboxamide, carboxamide, carboxy, 1-6C alkoxyalkyl, 1-6C alkylcarboxyl or 1-6C

carboxyalkyl) or one of R3' and R4' + one of R1' + R2' + N = 5- or 6- heterocyclyl; R5' = halo, H, 1-6C alkyl or 1-6C alkoxy; R6' = a group of formula (i);

Y = O or NR8'; R8' = H or 1-6C alkyl and R7' = H, halo, 1-6C haloalkyl or 1-6C alkoxy.
INDEPENDENT CLAIMS are included for the following:
(1) use of an Ih modulation assay for indentifying compounds useful for treating and preventing psychiatric disorders and
(2) new compounds of formula (I) and their salts and solvates.
A = a group of formula (a)-(c);
Y = CH or N;
X = O, S, CH=CH or CH=N;
P, S = H, 1-4C alkyl, 1-3C alkoxy, cyano, halo, trifluoromethyl, phenyl or pyrrole (both optionally substituted by halo or 1-3C alkyl) or PC=CS = 1,2-phenylene, pyridinediyl (including 2, 3- or 3, 4-pyridinediyl) or 1-cyclohexen-1,2-diyl (all optionally substituted by one or more 1-4C alkyl, 1-4C alkoxy, cyano, halo, trifluoromethyl or phenyl or pyrrole (both optionally substituted by halo or 1-3C alkyl));
R1 = one or more H, 1-4C alkyl, 1-3C alkoxy, cyano, halo, trifluoromethyl, phenyl or pyrrole (both optionally substituted by halo or 1-3C alkyl);
B = a bivalent group derived from an aromatic group of formula (d)-(f);
Z' = O or S;
W = O, S or CH=CH;
R3-R5 = H, 1-4C alkyl or halo or R3 + R4 = a C-C bond;
n = 0 or 1;
provided that when A is (b), in which PC=CS form 1,2-phenylene optionally substituted by one or more 1-4C alkyl, 1-4C alkoxy, cyano, halo, trifluoromethyl or phenyl or pyrrole (both optionally substituted by

halo or 1-3C alkyl) and n = 0, then B = (e) or (f).
ACTIVITY - Antidepressant; anxiolytic; antipsychotic.
MECHANISM OF ACTION - ***IH*** channels*** modulator.
In vivo activity of 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-alpha -2-propenyl-benzenemethanamine (Z)-butenedioate (Ia) was measured as inhibition of mice burying behavior which correlated with ***IH*** channels*** modulation. (Ia) exhibited an ED50 value 3.2 mg/kg.
USE - Used in the manufacture of medicaments and in assays to identify compounds for treatment and prevention of psychiatric disorders including depression, anxiety and psychosis, anxiety disorders (phobic neuroses, panic neuroses, anxiety neuroses, post-traumatic stress disorder and acute stress disorder), attention-deficit disorders, eating disorders (obesity, anorexia nervosa and bulimia), personality disorders (borderline personality disorders), schizophrenia and other psychotic disorders (schizo-affective disorders, delusional disorders, shared psychotic disorder, brief psychotic disorder and psychotic disorder), narcolepsy-cataplexy syndrome, substance-related disorders and sexual function disorders.
Dwg.0/0

L2 ANSWER 42 OF 68 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-527472 [44] WPIDS
DOC. NO. NON-CPI: N1999-390689
DOC. NO. CPI: C1999-154966

TITLE: New nucleic acid encoding an ***IH*** channels*** ion*** channels***, used to identify specific modulators, and for treatment, prevention and diagnosis of e.g. cardiac disease.

DERWENT CLASS: B04 D16 S03
INVENTOR(S): BAUMANN, A; BOENIGK, W; GAUSS, R; KAUPP, U B; SCHOLTEN, A; SEIFERT, R; KAUPP, B

PATENT ASSIGNEE(S): (KERJ) FORSCHUNGSZENTRUM JUELICH GMBH

COUNTRY COUNT: 21

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9942574	A1	19990826 (199944)*	GE	81	
RW:	AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE W: JP US DE 19806581 A1 19991021 (199950) EP 1054963 A1 20001129 (200063) GE R: CH DE DK FR GB LI NL SE JP 2002507394 W 20020312 (200220) 80				

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9942574	A1	WO 1999-EP942	19990212
DE 19806581	A1	DE 1998-19806581	19980217
EP 1054963	A1	EP 1999-907550	19990212
		WO 1999-EP942	19990212
JP 2002507394 W		WO 1999-EP942	19990212
		JP 2000-532514	19990212

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1054963	A1 Based on	WO 9942574
JP 2002507394 W	Based on	WO 9942574

PRIORITY APPLN. INFO: DE 1998-19806581 19980217
AN 1999-527472 [44] WPIDS

NOVELTY - Nucleic acid (I), preferably DNA, encoding an ***Ih***

ion - ***channel***, or part of it, and the complements of (I), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) nucleic acid (Ia) at least 80% homologous with (I);
 - (2) ***Ih*** ***ion*** - ***channel*** polypeptide (II) encoded by (I);
 - (3) method for identifying agents (A) that modulate the activity of ion channels by contacting test compounds with (I) or (II);
 - (4) kits for the process of (3);
 - (5) pharmaceutical composition containing (I) and/or (II);
 - (6) construct containing (I);
 - (7) host cells containing this construct;
 - (8) antibodies (Ab) reactive with (II); and
 - (9) nucleic acid probes specific for (I).
- ACTIVITY - Analgesic; cardioactive.
MECHANISM OF ACTION - The ***Ih*** ***channel*** participates

in the pacemaker function in cardiac muscle.

USE - (I) and/or proteins (II) expressed by it are used to identify substances (A) that modulate activity of ion channels; to treat and/or diagnose ion channel-related diseases, particularly cardiac or circulatory disorders and to prevent and/or treat cardiac/circulatory disorders (especially faulty regulation of the sinus ganglion), sleep disorders (particularly abnormal function of cortico-thalamic neurons) and/or pain.

Fragments of (I) are used to detect mutations in (I), e.g. for differential diagnosis.
Dwg.0/6

L2 ANSWER 43 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:147465 BIOSIS

DOCUMENT NUMBER: PREV200000147465

TITLE: A novel role of the Ih current in regulating the frequency of the respiratory rhythm in mice.

AUTHOR(S): Toboy-Brisson, M. (1); Telgkamp, P. (1); Ramirez, J. M. (1)
CORPORATE SOURCE: (1) Dept. Anatomy and Comm. Neurobiology, University of

Chicago, Chicago, IL, 60637 USA
SOURCE: Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 1909.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999

Society for Neuroscience
ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L2 ANSWER 44 OF 68 MEDLINE DUPLICATE 21

ACCESSION NUMBER: 1999388102 MEDLINE

DOCUMENT NUMBER: 99388102 PubMed ID: 10457065

TITLE: Modulation of the hyperpolarization-activated cation current of rat thalamic relay neurons by intracellular pH.

AUTHOR: Munsch T; Pape H C
CORPORATE SOURCE: Otto-von-Guericke Universitat, Medizinische Fakultat,

Institut fur Physiologie, Leipzigerstrasse 44, D-39120 Magdeburg, Germany.

thomas.munsch@medizin.uni-magdeburg.de
SOURCE: JOURNAL OF PHYSIOLOGY, (1999 Sep 1) 519 Pt 2 493-504.

Journal code: 0266262. ISSN: 0022-3751.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199911

ENTRY DATE: Entered STN: 20000111

Last Updated on STN: 20000111

Entered Medline: 19991122

AB 1. Properties of the hyperpolarization-activated cation current (Ih) were

investigated in thalamocortical neurones of an in vitro slice preparation of the rat ventrobasal thalamic complex (VB) before and during changes of

pipette pH (pHp), intracellular pH (pHi) and bath pH (pHb) using the whole-cell patch-clamp technique and fluorescence ratio imaging of the

pH indicator 2',7-bis(carboxyethyl)-5-(and -6)-carboxyfluorescein (BCECF). 2.

Recording of Ih with predefined pHp revealed significant shifts in the voltage dependence of Ih activation (V) of 4-5 mV to more positive values

for a pHp of 7.5 and 2-3 mV to more negative values for a pHp of 6.7 as

compared to control values (pHp = 7.1). 3. Application of the weak acid

lactate (20 mM), which produced a slow monophasic intracellular acidification, induced a reversible negative shift of V of up to 3 mV.

Application of 20 mM TMA, which caused a distinct intracellular alkalinization, shifted V to 4-5 mV more positive values. 4. In slices bathed in Hepes-buffered saline, no significant pHo dependence of Ih was

observed. Changing pHo by altering the extracellular [HCO3-] in the

presence of constant pCO2 also revealed no significant pHo dependence of

Ih. 5. Rhythmic stimulation of thalamocortical neurones with repetitive depolarizing pulse trains caused an intracellular acidification, which reversibly decreased the amplitude and time course of activation of Ih.

6. The results of the present study indicate that shifts in pHi result in a significant modulation of the gating properties of ***Ih*** ***channels*** in TC neurones. Through this mechanism activity-dependent shifts in pHi may contribute to the up- and downregulation of Ih.

presence of constant pCO2 also revealed no significant pHo dependence of

Ih. 5. Rhythmic stimulation of thalamocortical neurones with repetitive depolarizing pulse trains caused an intracellular acidification, which reversibly decreased the amplitude and time course of activation of Ih.

6. The results of the present study indicate that shifts in pHi result in a significant modulation of the gating properties of ***Ih*** ***channels*** in TC neurones. Through this mechanism

activity-dependent shifts in pHi may contribute to the up- and downregulation of Ih.

L2 ANSWER 45 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:775595 CAPLUS
DOCUMENT NUMBER: 132:146537

TITLE: Chronic morphine increases GABA tone on serotonergic

neurons of the dorsal raphe nucleus: association with an up-regulation of the cyclic AMP pathway

AUTHOR(S): Jolas, T.; Nestler, E. J.; Aghajanian, G. K.
CORPORATE SOURCE: Ribicoff Research Facilities, Department of Psychiatry

and Pharmacology, Connecticut Mental Health Center, Yale University School of Medicine, New Haven, CT, USA

SOURCE: Neuroscience (Oxford) (1999), Volume Date 2000, 95(2), 433-443

CODEN: NRSCDN; ISSN: 0306-4522

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Major adaptations after chronic exposure to morphine include an up-regulation of the adenosine 3',5'-monophosphate pathway. Acute

opioids, via mu-opioid receptors, disinhibit midbrain serotonergic neurons by suppressing inhibitory GABAergic transmission in the dorsal raphe nucleus and adjacent periaqueductal gray. This study examd.

whether chronic morphine induces a compensatory increase in GABA inputs to 5-hydroxytryptamine neurons and whether this was assoc. with an up-regulation of the adenosine 3',5'-monophosphate pathway. The

firing rate of serotonergic neurons was reduced in brain slices from morphine-dependent rats, an effect reversed by the GABAA antagonist bicuculline. The retn. in firing rate was accompanied by an increased frequency of spontaneous GABAergic inhibitory postsynaptic currents, indicating increased GABA tone in the slice. The increase in GABA

tone in brain slices from dependent rats was assoc. with increased induction of inhibitory postsynaptic currents by the adenylyl cyclase activator forskolin, suggesting an up-regulation of the adenosine 3',5'-monophosphate pathway. Indeed, chronic morphine increased

levels of adenylyl cyclase VIII (but not of adenylyl cyclase I, III or V) immunoreactivity in the dorsal raphe nucleus area. Two adenosine 3',5'-monophosphate-mediated mechanisms for the increase in GABA

tone were discerned. The first, which predominated when impulse-flow was blocked by tetrodotoxin, involves protein kinase A since it was sensitive to protein kinase A inhibitors. The second, seen when impulse-flow was intact

(i.e. absence of tetrodotoxin), was insensitive to protein kinase A inhibitors but was suppressed by ZD7288, a blocker of hyperpolarizing-activated ***Ih*** ***channels*** which are directly activated by

adenosine 3',5'-monophosphate. We conclude that chronic morphine induces an up-regulation of the adenosine 3',5'-monophosphate pathway in

GABAergic inputs to serotonergic cells, resulting in an increase in spontaneous and impulse-flow dependent GABA release. These changes would lead to an

increase in GABA tone and subsequently to the reported decrease in serotonergic activity during opiate withdrawal.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE

RE FORMAT

L2 ANSWER 46 OF 68 MEDLINE DUPLICATE 22

ACCESSION NUMBER: 1999255497 MEDLINE

DOCUMENT NUMBER: 99255497 PubMed ID: 10320738

TITLE: Common components of patch-clamp internal recording solutions can significantly affect protein kinase A activity.

AUTHOR: Vargas G; Yeh T Y; Blumenthal D K; Lucero M T
CORPORATE SOURCE: Department of Physiology, University of Utah, School of

Medicine, Salt Lake City, UT 84108, USA.

CONTRACT NUMBER: R01 #DC02994-02 (NIDCD)

SOURCE: BRAIN RESEARCH, (1999 May 15) 828 (1-2) 169-73.

Journal code: 0045503. ISSN: 0006-8993.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 19990714

Last Updated on STN: 19990714

Entered Medline: 19990630

AB Common components of whole-cell internal recording solutions were tested

both in vitro and in patch-clamp experiments for their effects on the

activity of cAMP-dependent protein kinase. Potassium fluoride (KF), 440 mM

trimethylamine chloride and exclusion of bovine serum albumin (BSA) decreased the activity of the enzyme, while ethylene glycol-bis (beta-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA) and the potassium salts of aspartate, gluconate, methylsulfate and monobasic phosphate increased its activity. Addition of KF to the internal solution produced a hyperpolarizing shift in the V1/2 of ***Ih*** ***channel*** activation, consistent with the KF-induced reduction

of protein kinase A activity. Therefore, consideration of the composition of internal solutions is warranted when studying channel physiology by patch-clamp techniques.

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trimethylamine chloride and exclusion of bovine serum albumin (BSA) decreased the activity of the enzyme, while ethylene glycol-bis (beta-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA) and the potassium salts of aspartate, gluconate, methylsulfate and monobasic phosphate increased its activity. Addition of KF to the internal solution produced a hyperpolarizing shift in the V1/2 of ***Ih*** ***channel***

activation, consistent with the KF-induced reduction of protein kinase A activity. Therefore, consideration of the composition of

internal solutions is warranted when studying channel physiology by patch-clamp techniques.

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L2 ANSWER 47 OF 68 MEDLINE DUPLICATE 23

ACCESSION NUMBER: 1999244729 MEDLINE

DOCUMENT NUMBER: 99244729 PubMed ID: 10226155

TITLE: Elevation of intracellular Na+ induced by hyperpolarization

at the dendrites of pyramidal neurones of mouse hippocampus.

AUTHOR: Tsubokawa H; Miura M; Kano M
CORPORATE SOURCE: Laboratory for Cellular Neurophysiology, Brain Science

Institute, RIKEN, Wako, Saitama 351-0198, Japan..

neuron@ijichi.ac.jp

SOURCE: JOURNAL OF PHYSIOLOGY, (1999 May 15) 517 (Pt 1) 135-42.

Journal code: 0266262. ISSN: 0022-3751.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907

ENTRY DATE: Entered STN: 19990727

Last Updated on STN: 19990727

Entered Medline: 19990712

AB 1. Whole-cell recordings were made from CA1 pyramidal cells in mouse

hippocampal slices with patch pipettes containing the sodium indicator dye SBFI (sodium binding benzofuran isophthalate). Using a high-speed

imaging system, we investigated changes in intracellular sodium concentration, [Na+]i, in response to hyperpolarizing pulses applied to the soma. 2. In

current-clamp recordings, we detected increases in [Na+]i during negative

current injection. Hyperpolarization-induced [Na+]i elevation was more prominent in the middle apical dendrites than in the soma. 3. In the

voltage-clamp mode, hyperpolarization induced rapid increases in [Na+]i at

the apical dendrites that were significantly faster than those at the soma. The signals were not affected by bath application of 1 microM

TTX, but were reduced by 5 mM CsCl. 4. Changes in membrane potential recorded from the apical dendrites in response to negative currents were

significantly smaller than those recorded from the soma. In the presence of 5 mM CsCl, the I-V relationships measured at the soma and the

dendrites became almost identical, indicating that CsCl-sensitive components are predominantly in the apical dendrites. 5. These results suggest that

hyperpolarization-induced [Na+]i elevations reflect Na+ influx through the

non-selective cation channel (***Ih*** ***channel***), and that this channel is distributed predominantly in the apical dendrites. The

non-uniform Na+ influx may contribute to integrative functions of the dendrites.

L2 ANSWER 48 OF 68 MEDLINE DUPLICATE 24

ACCESSION NUMBER: 2000114425 MEDLINE

DOCUMENT NUMBER: 20114425 PubMed ID: 10651003

TITLE: Physiological significance of hyperpolarization-activated inward currents (Ih) in smooth muscle cells from the

circular layers of pregnant rat myometrium.

AUTHOR: Okabe K; Inoue Y; Kawarabayashi T; Kajiya H; Okamoto F;

Soeda H

CORPORATE SOURCE: Department of Oral Physiology, Fukuoka Dental College,

Japan.. okapi@college.fdcnet.ac.jp

SOURCE: PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1999 Dec)

439 (1-2) 76-85.

Journal code: 0154720. ISSN: 0031-6768.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000314

Last Updated on STN: 20000314

Entered Medline: 20000302

AB The properties of hyperpolarization-activated current in pregnant rat uterus (17-19 days gestation) were investigated using microelectrode and

patch-clamp techniques, and isometric tension recording. The resting membrane potentials were -58.4 mV and -48.5 mV in longitudinal and circular muscle cells, respectively. Application of hyperpolarizing current pulses produced a time-dependent anomalous inward

rectification of membrane potential only in circular muscle cells. Under voltage-clamp

conditions, inward currents (Ih) were activated by long hyperpolarizing pulses below -60 mV in circular but not in longitudinal muscle cells. Application of extracellular but not intracellular Cs⁺ reduced the amplitude of Ih in a concentration-dependent manner (an IC50 of 0.15 mM). The reversal potential for Ih was -26.2 mV and the slope conductance was 5 nS/pF. Changes in [K⁺]_o and [Na⁺]_o shifted the reversal potential, and Ih amplitude increased with excess [K⁺]_o and decreased with low [Na⁺]_o. The steady-state activation of Ih was well fitted by a Boltzmann equation with a half-activation potential of -84.3 mV and a slope factor of 9.6 mV. Time courses of activation and deactivation of the current strongly depended on membrane potential, and were well fitted by a single exponential function. The activation time constant of Ih was dependent on temperature. In isometric tension recording, application of extracellular Cs⁺ to the circular muscles reduced the frequency, but not the amplitude, of spontaneous contractions in a concentration-dependent manner. It is concluded that in pregnant rat uterus ***Ih*** **channels*** are predominantly distributed in smooth muscle cells from the circular layer. Since Ih is activated at the resting membrane potential, it is likely that this current contributes to the maintenance of resting membrane potential and spontaneous activity in circular smooth muscle cells of late pregnant rats.

L2 ANSWER 49 OF 68 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 25
ACCESSION NUMBER: 2001:90791 BIOSIS
DOCUMENT NUMBER: PREV200100090791
TITLE: Molecular cloning of a putative voltage- and cyclic nucleotide-gated ion channel present in the antennae and eyes of *Drosophila melanogaster*.
AUTHOR(S): Marx, Thomas; Gisselmann, Guenter; Stoerkuhl, Klemens F.; Hovemann, Bernhard T.; Hatt, Hanns (1)
CORPORATE SOURCE: (1) Fakultät fuer Biologie, Lehrstuhl fuer Zellphysiologie, ND4, Ruhr-Universität-Bochum, Universitätsstr. 150, D-44780, Bochum; hanns.hatt@ruhr-uni-bochum.de Germany
SOURCE: Invertebrate Neuroscience, (1999) Vol. 4, No. 1, pp. 55-63.
print.
ISSN: 1354-2516.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The amino acid sequence BCNG-1 (brain cyclic nucleotide gated 1, of the mouse), the first member of mammalian ***Ih*** **channels***, was used to construct a set of polymerase chain reaction (PCR) primers from possibly conserved regions. Reverse transcription-PCR with *Drosophila melanogaster* mRNA yielded a PCR product, which exhibited a high homology to BCNG-1. Using these PCR products to screen a *D. melanogaster* head cDNA library we isolated a cDNA encoding a member of a new class of putative voltage- and cyclic nucleotide-gated potassium channels from *D. melanogaster*. The most important features of the amino acid sequence predicted from the cDNA were a C-terminal cyclic nucleotide-binding region, an S4-voltage sensor and a putative potassium-selective pore-forming motif. The high homology of 51% to the sea urchin ***Ih*** **channel***, which belongs to the same class of ion channels as BCNG-1, leads us to suggest that the *Drosophila* cDNA is the first insect member of a new class of hyperpolarization-activated and cyclic nucleotide-gated channels. As shown by in situ hybridization, a pronounced mRNA expression was detected in neuronal tissue, including sensory tissue like the compound eyes, and the olfactory and the auditory organs.

L2 ANSWER 50 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:586704 CAPLUS
DOCUMENT NUMBER: 129:327505
TITLE: Molecular identification of a hyperpolarization-activated (***Ih***) ***ion*** **channel*** in sperms of sea urchin
AUTHOR(S): Gauss, Renate
CORPORATE SOURCE: Inst. Biologische Informationsverarbeitung, Forschungszentrum Juelich G.m.b.H., Juelich, D-52425, Germany
SOURCE: Berichte des Forschungszentrums Juelich (1998), Juel-3547, 1-98 pp.
CODEN: FJBEE5; ISSN: 0366-0885
DOCUMENT TYPE: Report
LANGUAGE: German
AB A hyperpolarization-activated (***Ih***) ***ion*** **channel*** was cloned out of the gonads of the sea urchin *Strongylocentrotus purpuratus*. Degenerated primers were deduced by sequence comparisons of different cyclic nucleotide-binding sites. With these primers a PCR fragment was amplified. The complete cDNA was isolated out of a

cDNA library. The tissue-specific expression of the *S. purpuratus* gene was investigated in Northern blot analyses. Two different transcripts were found with sizes according to those of the isolated cDNA. Specific antibodies were generated for the localization of the channel protein in sea urchin sperms. Immunocytochem. studies revealed that the channel protein is expressed in the flagella. Western blot analyses with sepd. head- and flagella-fractions confirmed this result. The amino acid sequence has 6 transmembranous segments, a pore region, and a binding site for cyclic nucleotides. The functional characterization of the expressed channel protein revealed that the ion channel is voltage-dependent and that the membrane is opened after hyperpolarization. The binding of cAMP to the channel protein changes the time process and the amplitude of the influx by increasing the probability of opening. The ion channel is only weak K⁺-selective. The relative permeability of the different ions is influenced by the extracellular K⁺-concn. The flux through the ion channel is blocked by small amts. of extracellular Cs⁺-ions voltage-dependently.

L2 ANSWER 51 OF 68 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 1998414534 MEDLINE
DOCUMENT NUMBER: 98414534 PubMed ID: 9742133
TITLE: Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons.
AUTHOR: Magee J C
CORPORATE SOURCE: Neuroscience Center, Louisiana State University Medical Center, New Orleans, Louisiana 70112, USA.. jmagee@lsu.edu
CONTRACT NUMBER: NS35865 (NINDS)
SOURCE: JOURNAL OF NEUROSCIENCE, (1998 Oct 1) 18 (19) 7613-24.
Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

AB Step hyperpolarizations evoked slowly activating, noninactivating, and slowly deactivating inward currents from membrane patches recorded in the cell-attached patch configuration from the soma and apical dendrites of hippocampal CA1 pyramidal neurons. The density of these hyperpolarization-activated currents (Ih) increased over sixfold from soma to distal dendrites. Activation curves demonstrate that a significant fraction of ***Ih*** **channels*** is active near rest and that the range is hyperpolarized relatively more in the distal dendrites. Ih activation and deactivation kinetics are voltage- and temperature-dependent, with time constants of activation and deactivation decreasing with hyperpolarization and depolarization, respectively. Ih demonstrated a mixed Na⁺-K⁺ conductance and was sensitive to low concentrations of external CsCl. Dual whole-cell recordings revealed regional differences in input resistance (Rin) and membrane polarization rates (taumem) across the somatodendritic axis that are attributable to the spatial gradient of ***Ih*** **channels***. As a result of these membrane effects the propagation of subthreshold voltage transients is directionally specific. The elevated dendritic Ih density decreases EPSP amplitude and duration and reduces the time window over which temporal summation takes place. The backpropagation of action potentials into the dendritic arborization was impacted only slightly by dendritic Ih, with the most consistent effect being a decrease in dendritic action potential duration and an increase in afterhyperpolarization. Overall, Ih acts to dampen dendritic excitability, but its largest impact is on the subthreshold range of membrane potentials where the integration of inhibitory and excitatory synaptic inputs takes place.

L2 ANSWER 52 OF 68 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 1998130653 MEDLINE
DOCUMENT NUMBER: 98130653 PubMed ID: 9463440
TITLE: Substance P regulates Ih via a NK-1 receptor in vagal sensory neurons of the ferret.
AUTHOR: Jafri M S; Weinreich D
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, University of Maryland, School of Medicine, Baltimore, Maryland 21201-1559, USA.
CONTRACT NUMBER: NS-22069 (NINDS)
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1998 Feb) 79 (2) 769-77.
Journal code: 0375404. ISSN: 0022-3077.
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DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
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ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
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Entered Medline: 19980414

AB Substance P (SP) hyperpolarizes approximately 80% of ferret vagal sensory neurons (nodose ganglion neurons) via NK-1 receptor-mediated activation of a potassium current (IK). A depolarizing current activated by membrane hyperpolarization could minimize the SP-induced hyperpolarization. Such a current exists in 65% of the nodose neurons (n = 264). In this study, we examine this current and how it can interact with SP-induced membrane hyperpolarizations. This slowly developing, noninactivating inward current, designated Ih, was activated maximally at about -120 mV and had a reversal potential value of -23 +/- 4.4 mV (n = 4). The time course of activation followed voltage-dependent, monoexponential kinetics. Steady-state activation curves derived from tail current analysis were well fit by a Boltzmann equation yielding a half-activation potential (V1/2) of -77 +/- 1.5 mV and a ks value of 18 +/- 0.5 (n = 8). In the presence of 1 mM cesium, the current was completely abolished. These parameters are consistent with those derived for Ih in other neurons. Substance P (200 nM) reduced the magnitude of Ih elicited by membrane hyperpolarizations to about -110 mV but did not affect the magnitude of Ih elicited by hyperpolarizations to more negative potentials. Tail current analysis revealed that this effect was the result of a SP-induced shift of the Ih activation curve to more negative membrane potentials. The V1/2 value for Ih was shifted by -20 +/- 1.4 mV in the presence of SP with no change in ks (18 +/- 0.7; n = 5). The SP effect on Ih, like its effect on IK, was blocked reversibly by 10 nM CP99,994, a NK-1 antagonist, and was mimicked by the NK-1 agonist Ac-[Arg6, Sar9, Met(O2)11]SP(6-11) (ASMSP; 200 nM). Ih was not affected by NK-2 or NK-3 selective agonists (n = 4 for each) nor was the effect of SP on Ih reduced by an NK-2 antagonist (n = 4). These results show that SP activates a NK-1 receptor coupled to the ***Ih*** **channel***. Thus NK-1 receptor activation in ferret vagal afferents not only leads to membrane hyperpolarization but it also can enhance synergistically this inhibitory effect by decreasing Ih.

L2 ANSWER 53 OF 68 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 1998295993 MEDLINE
DOCUMENT NUMBER: 98295993 PubMed ID: 9634236
TITLE: A family of hyperpolarization-activated mammalian cation channels.
AUTHOR: Ludwig A; Zong X; Jeglitsch M; Hofmann F; Biel M
CORPORATE SOURCE: Institut für Pharmakologie und Toxikologie, Technische Universität München, Germany.
SOURCE: NATURE, (1998 Jun 11) 393 (6685) 587-91.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ225122; GENBANK-AJ225123; GENBANK-AJ225124
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980702

AB Pacemaker activity of spontaneously active neurons and heart cells is controlled by a depolarizing, mixed Na⁺/K⁺ current, named Ih (or If) in the sinoatrial node of the heart). This current is activated on hyperpolarization of the plasma membrane. In addition to depolarizing pacemaker cells, Ih is involved in determining the resting membrane potential of neurons and provides a mechanism to limit hyperpolarizing currents in these cells. Hormones and neurotransmitters that induce a rise in cyclic AMP levels increase Ih by a mechanism that is independent of protein phosphorylation, and which involves direct binding of the cyclic nucleotide to the channel that mediates Ih. Here we report the molecular cloning and functional expression of the gene encoding a hyperpolarization-activated cation channel (HAC1) that is present in brain and heart. This channel exhibits the general properties of ***Ih*** **channels***. We have also identified full-length sequences of two related channels, HAC2 and HAC3, that are specifically expressed in the brain, indicating the existence of a family of hyperpolarization-activated cation channels.

L2 ANSWER 54 OF 68 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 1998295992 MEDLINE
DOCUMENT NUMBER: 98295992 PubMed ID: 9634235
TITLE: Molecular identification of a hyperpolarization-activated channel in sea urchin sperm.
AUTHOR: Gauss R; Seifert R; Kaupp U B
CORPORATE SOURCE: Institut für Biologische Informationsverarbeitung, Forschungszentrum Jülich, Germany.
SOURCE: NATURE, (1998 Jun 11) 393 (6685) 583-7.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Y16880
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716

Entered Medline: 19980702

AB Sea urchin eggs attract sperm through chemotactic peptides, which evoke complex changes in membrane voltage and in the concentrations of cyclic AMP, cyclic GMP and Ca²⁺ ions. The intracellular signalling pathways and their cellular targets are largely unknown. We have now cloned, from sea urchin testis, the complementary DNA encoding a channel polypeptide, SPIH. Functional expression of SPIH gives rise to weakly K⁺-selective hyperpolarization-activated channels, whose activity is enhanced by the direct action of cAMP. Thus, SPIH is under the dual control of voltage and cAMP. The SPIH channel, which is confined to the sperm flagellum, may be involved in the control of flagellar beating. SPIH currents exhibit all the hallmarks of hyperpolarization-activated currents (I_h), which participate in the rhythmic firing of central neurons, control pacemaking in the heart, and curtail saturation by bright light in retinal photoreceptors. Because of their sequence and functional properties, ***I_h*** ***channels*** form a class of their own within the superfamily of voltage-gated and cyclic-nucleotide-gated channels.

L2 ANSWER 55 OF 68 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 1998387600 MEDLINE
DOCUMENT NUMBER: 98387600 PubMed ID: 9722145
TITLE: Hyperpolarization-activated inward currents contribute to spontaneous electrical activity and CO₂/H⁺ sensitivity of cultivated neurons of fetal rat medulla.
AUTHOR: Wellner-Kienitz M C; Shams H
CORPORATE SOURCE: Institut für Physiologie, Ruhr-Universität Bochum, Germany.
SOURCE: NEUROSCIENCE, (1998 Nov) 87 (1) 109-21.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981026

AB Neurons growing out from cultivated fetal medullary slices that exhibited spontaneous electrical activity after blockade of synaptic transmission were investigated by the patch-clamp technique for their response to decreases in the extracellular pH. Increases in the [H⁺], induced by increases in pCO₂, resulted in a decrease in spike frequency associated with a decrease in the rate of depolarization preceding each action potential. The type of ion channel, contributing to interspike depolarization, and which may therefore be the site of CO₂/H⁺ action, was identified by application of agents that inhibited the hyperpolarization-activated cation, ***I_h***, ***channel*** (Cs⁺ and ZD7288). Application of Cs⁺ and ZD7288 slightly hyperpolarized the cell membrane, decreased the interspike slope and inhibited CO₂/H⁺-induced modulations of spike frequency in one group of CO₂-inhibited medullary neurons, suggesting that I_h contributes to spontaneous neuronal activity and to CO₂/H⁺-sensitivity. CO₂/H⁺ effects on I_h were further confirmed in voltage-clamp experiments. Increasing the bath CO₂ from 2% to 9% reduced the I_h amplitude, shifted the mean E_h from -54 to -60 mV, lengthened the voltage-dependent delay of current activation and increased the time-constants of activation at all potentials studied. It is concluded that depolarizing inward currents through ***I_h*** ***channels*** participate in the gradual ramp-like change in membrane potential which depolarizes the cell up to the threshold of Na⁺ spike generation. CO₂/H⁺-induced inhibition of I_h reduces the contribution of this ion current to the interspike depolarization and accounts for the CO₂/H⁺-induced decrease in spike frequency in one type of CO₂/H⁺-inhibited medullary cells.

L2 ANSWER 56 OF 68 MEDLINE DUPLICATE 31
ACCESSION NUMBER: 97368685 MEDLINE
DOCUMENT NUMBER: 97368685 PubMed ID: 9225299
TITLE: Modulation of I_h by 5-HT in neonatal rat motoneurons in vitro: mediation through a phosphorylation independent action of cAMP.
AUTHOR: Larkman P M; Kelly J S
CORPORATE SOURCE: Department of Pharmacology, University of Edinburgh, U.K..
P.Larkman@ed.ac.uk
SOURCE: NEUROPHARMACOLOGY, (1997 Apr-May) 36 (4-5) 721-33.
Journal code: 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970926
Last Updated on STN: 20000303

Entered Medline: 19970915

AB The depolarization of adult and neonatal rat facial and spinal motoneurons by 5-hydroxytryptamine (5-HT) in part involves an enhancement of the hyperpolarization-activated, inward-rectifier, I_h. Under experimental conditions which promote this action, 5-HT evokes an inward current which can be mimicked by intracellularly applied adenosine 3',5'-cyclic monophosphate (cAMP) and potentiated by the cAMP-specific phosphodiesterase inhibitor Ro 20-1724. In this study, we show that this action of 5-HT can be blocked by the adenylyl cyclase inhibitors 2',3'-dideoxyadenosine (2',3'-DDA), 5'-adenylylimidodiphosphate (AMP-PNP) and SQ-22536 (9-(tetrahydro-2-furyl)adenine), but not by external or internal application of the protein kinase inhibitors H-7, staurosporine and chelerythrine. The most recently cloned 5-HT receptor subtypes, 5-HT₄, 5-HT₆ and 5-HT₇, can all stimulate adenylyl cyclase when activated. In the presence of internal GTP-gamma-S, 5-HT irreversibly enhanced I_h. The 5-HT-induced inward current could be reversibly blocked by methysergide, but not by the 5-HT₄ receptor antagonist GR-113808A, the 5-HT₆ and 5-HT₇ antagonist clozapine and the 5-HT_{1A} antagonist WAY-100365. 5-Methoxytryptamine (5-MeOT) and 5-carboxamidotryptamine (5-CT) mimicked the action of 5-HT with a rank order of potency of 5-HT = 5-MeOT > 5-CT. Surprisingly, 8-hydroxy-2-(di-N-propylamino)-tetralin (8-OH DPAT), a 5-HT_{1A} and 5-HT₇ agonist was inactive on facial motoneurons unlike its reported agonist action on spinal motoneurons. It is proposed that cAMP produced by 5-HT-mediated stimulation of adenylyl cyclase acts in a phosphorylation-independent manner, possibly directly, on the ***I_h*** ***channel***. The 5-HT receptor subtype mediating this response cannot be correlated with any of the classified 5-HT receptor subtypes that stimulate adenylyl cyclase.

L2 ANSWER 57 OF 68 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 97384762 MEDLINE
DOCUMENT NUMBER: 97384762 PubMed ID: 9242273
TITLE: Modification of current transmitted from apical dendrite to soma by blockade of voltage- and Ca²⁺-dependent conductances in rat neocortical pyramidal neurons.
AUTHOR: Schwandt P C; Crill W E
CORPORATE SOURCE: Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle 98195-7290, USA.
CONTRACT NUMBER: NS-16792 (NINDS)
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1997 Jul) 78 (1) 187-98.
Journal code: 0375404. ISSN: 0022-3077.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971202

AB The axial current transmitted to the soma during the long-lasting iontophoresis of glutamate at a distal site on the apical dendrite was measured by somatic voltage clamp of rat neocortical pyramidal neurons. Evidence for voltage- and Ca²⁺-gated channels in the apical dendrite was sought by examining the modification of this transmitted current resulting from the alteration of membrane potential and the application of channel-blocking agents. After N-methyl-D-aspartate receptor blockade, iontophoresis of glutamate on the soma evoked a current whose amplitude decreased linearly with depolarization to an extrapolated reversal potential near 0 mV. Under the same conditions, glutamate iontophoresis on the apical dendrite 241-537 microm from the soma resulted in a transmitted axial current that increased with depolarization over the same range of membrane potential (about -90 to -40 mV). Current transmitted from dendrite to soma was thus amplified during depolarization from resting potential (about -70 mV) and attenuated during hyperpolarization. After Ca²⁺ influx was blocked to eliminate Ca²⁺-dependent K⁺ currents, application of 10 mM tetraethylammonium chloride (TEA) altered the amplitude and voltage dependence of the transmitted current in a manner consistent with the reduction of dendritic voltage-gated K⁺ current. We conclude that dendritic, TEA-sensitive, voltage-gated K⁺ channels can be activated by tonic dendritic depolarization. The most prominent effects of blocking Ca²⁺ influx resembled those elicited by TEA application, suggesting that these effects were caused predominantly by blockade of a dendritic Ca²⁺-dependent K⁺ current. When cells were impaled with

microelectrodes containing ethylene glycol-bis(beta-amino-ethyl ether)-N,N',N''-tetraacetic acid to prevent a rise in intracellular Ca²⁺ concentration, blockade of Ca²⁺ influx altered the tonic transmitted current in different manner consistent with the blockade of an inward dendritic current carried by high-threshold-activated Ca²⁺ channels. We conclude that the primary effect of Ca²⁺ influx during tonic dendritic depolarization is the activation of a dendritic Ca²⁺-dependent K⁺ current.

The hyperpolarizing attenuation of transmitted current was unaffected by blocking all known voltage-gated inward currents except the hyperpolarization-activated cation current (I_h). Extracellular Cs⁺ (3 mM) reversibly abolished both the hyperpolarizing attenuation of transmitted current and I_h measured at the soma. We conclude that activation of I_h by hyperpolarization of the proximal apical dendrite would cause less axial current to arrive at the soma from a distal site than in a passive dendrite. Several functional implications of dendritic K⁺ and ***I_h*** ***channels*** are discussed.

L2 ANSWER 58 OF 68 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 1998040434 MEDLINE
DOCUMENT NUMBER: 98040434 PubMed ID: 9374278
TITLE: Clonidine reduces hyperpolarization-activated inward current (I_h) in rat hypoglossal motoneurons.
AUTHOR: Parkis M A; Berger A J
CORPORATE SOURCE: Department of Physiology and Biophysics, School of Medicine, University of Washington, Seattle 98195-7290, USA.
CONTRACT NUMBER: HL-49657 (NHLBI)
SOURCE: BRAIN RESEARCH, (1997 Sep 19) 769 (1) 108-18.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980217

AB We used intracellular recording techniques to investigate the actions of clonidine on hypoglossal motoneurons (HMs) in rat brainstem slices. Clonidine (10-100 microM) produced a small (2-6 mV), dose-dependent hyperpolarization in HMs, accompanied by an increase in peak input resistance (R_N). It also slowed the time course of the depolarizing 'sag' of the voltage response to constant hyperpolarizing current steps. These effects were mimicked by the alpha2-adrenoceptor (alpha2-AR) agonist guanabenz, but not by the I_h-imidazoline receptor agonists moxonidine or rilmenidine. Recorded in single-electrode voltage clamp mode, clonidine decreased input conductance of HMs and reduced the amplitude of a hyperpolarization-activated inward current (I_h). Clonidine's effect on I_h was three-fold: it shifted the half-activation voltage (V_{1/2}) in the hyperpolarizing direction (by 4.4 +/- 0.7 mV at a dose of 10 microM), decreased the maximal current (by approximately 20%), and slowed the time course of I_h activation at all voltage steps. At the most hyperpolarized potential steps, clonidine slowed activation of I_h dramatically, yielding a striking increase in the activation time constant. The alpha2-AR antagonists yohimbine and idazoxan reduced clonidine's effect on V_{1/2} and on the I_h activation time course, but neither blocked clonidine's reduction of the maximal current, nor its strong slowing of I_h activation at the most hyperpolarized steps. We were unable to mimic or occlude clonidine's actions with the adenylyl cyclase inhibitor SQ 22536 nor with the non-specific protein kinase inhibitor H-7. We conclude that clonidine hyperpolarizes HMs via a reduction of the amount of I_h that is active at rest, and that the response is mediated in part by alpha2-ARs. Some effects of clonidine on these neurons do not appear to be receptor-mediated, and may be due to physical block by clonidine of ***I_h*** ***channels***.

L2 ANSWER 59 OF 68 MEDLINE DUPLICATE 34
ACCESSION NUMBER: 97434808 MEDLINE
DOCUMENT NUMBER: 97434808 PubMed ID: 9288676
TITLE: Lack of regulation by intracellular Ca²⁺ of the hyperpolarization-activated cation current in rat thalamic neurones.
AUTHOR: Budde T; Biella G; Munsch T; Pape H C
CORPORATE SOURCE: Otto-von-Guericke Universität, Medizinische Fakultät, Institut für Physiologie, Magdeburg, Germany.
SOURCE: JOURNAL OF PHYSIOLOGY, (1997 Aug 15) 503 (Pt 1) 79-85.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971021
Last Updated on STN: 19971021
Entered Medline: 19971007
AB 1. The regulation of the hyperpolarization-activated cation current, I_h, in thalamocortical neurones by intracellular calcium ions has been implemented in a number of mathematical models on the waxing and waning

behaviour of synchronized rhythmic activity in thalamocortical circuits. In the present study, the Ca²⁺ dependence of Ih in thalamocortical neurones was experimentally investigated by combining Ca²⁺ imaging and patch-clamp techniques in the ventrobasal thalamic complex (VB) in vitro.

2. Properties of Ih were analysed before and during rhythmic stimulation of Ca²⁺ entry by trains of depolarizing voltage pulses. Despite a significant increase in intracellular Ca²⁺ concentration ([Ca²⁺]_i) from resting levels of 74 ± 23 nM to 251 ± 78 nM upon rhythmic stimulation, significant differences in the voltage dependence of Ih activation did not occur (half-maximal activation at -86.4 ± 1.3 mV vs. -85.2 ± 2.9 mV; slope of the activation curve, 11.2 ± 2.4 mV vs. 12.5 ± 2.5 mV). Recording of Ih with predefined values of [Ca²⁺]_i (13.2 nM or 10.01 μM in the patch pipette) revealed no significant differences in the activation curve or the fully activated I-V relationship of Ih. 3. In comparison, stimulation of the intracellular cyclic adenosine monophosphate (cAMP) pathway induced a significantly positive shift in Ih voltage dependence of +5.1 ± 1.9 mV, with no alteration in the fully activated I-V relationship. 4. These data argue against a direct regulation of Ih by intracellular Ca²⁺, and particularly do not support a primary role of Ca(2+)-dependent modulation of the ***Ih*** ***channels*** in the waxing and waning of sleep spindle oscillations in thalamocortical neurones.

L2 ANSWER 60 OF 68 MEDLINE DUPLICATE 35
ACCESSION NUMBER: 96322980 MEDLINE
DOCUMENT NUMBER: 96322980 PubMed ID: 8756443
TITLE: Actions of substance P on rat neostriatal neurons in vitro.
AUTHOR: Aosaki T; Kawaguchi Y
CORPORATE SOURCE: Laboratory for Neural Circuits, Institute of Physical and Chemical Research (RIKEN), Aichi, Japan.
SOURCE: JOURNAL OF NEUROSCIENCE, (1996 Aug 15) 16 (16) 5141-53.
Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961213

AB Actions of substance P (SP) on the neostriatal neurons in vitro rat slice preparations were studied via whole-cell patch-clamp recording. Almost all large spiny neurons (cholinergic cells) and half of the low-threshold spike (LTS) cells (somatostatin/ NOS-positive cells) showed depolarization or an inward shift of the holding currents in response to bath-applied SP in a dose-dependent manner. In contrast, no responses were observed in fast-spiking (FS) cells (parvalbumin-positive cells) and medium spiny cells. Spike discharges followed by slow EPSPs/EPSCs were evoked by intrastratial electrical stimulation in the large spiny neurons. Pretreatment with [D-Arg1, D-Pro2, D-Trp7,9, Leu11]-SP, an antagonist of the SP receptor, reversibly suppressed the induction of the slow EPSPs/EPSCs and unmasked slow IPSCs. The SP-induced inward current, although almost unchanged even after the blockade of ***Ih*** ***channels*** and voltage-dependent Na⁺, Ca²⁺, and K⁺ channels, changed its amplitude according to the Na⁺ concentration used in both the large spiny neurons and LTS cells. Thus, the cation current could account for virtually all of the inward current at resting levels in both neurons. These results suggest that the firing of afferent neurons such as striatonigral medium spiny neurons, one of the possible sources of SP, would increase the firing probability of the two types of interneurons of the neostriatum by SP-receptor-mediated opening of tetrodotoxin-insensitive cation channels.

L2 ANSWER 61 OF 68 MEDLINE DUPLICATE 36
ACCESSION NUMBER: 96374363 MEDLINE
DOCUMENT NUMBER: 96374363 PubMed ID: 8780654
TITLE: Abolition of spindle oscillations by serotonin and norepinephrine in the ferret lateral geniculate and perigeniculate nuclei in vitro.
AUTHOR: Lee K H; McCormick D A
CORPORATE SOURCE: Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06510, USA.
SOURCE: NEURON, (1996 Aug) 17 (2) 309-21.
Journal code: 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025
Last Updated on STN: 19970203
Entered Medline: 19961011

AB The transition from sleep to waking is associated with the abolition of spindle waves in thalamocortical neurons and the GABAergic cells of the thalamic reticular/perigeniculate nuclei. We tested the possibility that norepinephrine (NE) and serotonin (5-HT) may abolish spindle wave

generation through an enhancement of the hyperpolarization-activated cation current Ih in thalamocortical neurons. Local application of agents known to enhance Ih, including 5-HT, NE, the adenylyl cyclase activator, forskolin, and the beta-adrenergic agonist, isoproterenol, to lamina A1 of the dorsal lateral geniculate nucleus resulted in an abolition of local spindle wave generation in thalamocortical neurons. The abolition of spindle waves was reversed by the local application of the ***Ih*** ***channel*** blocker, cesium. These results suggest that NE and 5-HT may abolish the generation of spindle waves through the modulation of Ih in thalamocortical neurons.

L2 ANSWER 62 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996159624 CAPLUS
DOCUMENT NUMBER: 124250335
TITLE: Effects of zatebradine (UL-FS 49) on the vertebrate retina
AUTHOR(S): Usui, Shiro; Kamiyama, Yoshimi; Ogura, Toshihiko; Kodama, Itsuo; Toyama, Junji
CORPORATE SOURCE: Information and Computer Sciences, Toyohashi University Technology, Japan
SOURCE: Recent Progress in Electropharmacology of the Heart, Proceedings of the International Satellite Symposium of the 59th Annual Scientific Meeting of the Japanese Circulation Society, Nagoya, Apr. 3-4, 1995 (1996), Meeting Date 1995, 37-46. Editor(s): Toyama, Junji; Hiraoka, Masayasu; Kodama, Itsuo. CRC: Boca Raton, Fla.
CODEN: 62LYAD
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors demonstrated that zatebradine (UL-FS 49), a blocker of the pacemaker current (Ih), modulates the light response properties of rod photoreceptors through a simulation study with an ionic current model. Since Ih plays a major role in shaping the light response of the photoreceptor, the side effects induced by zatebradine can be explained by blocking ***Ih*** ***channels*** on the photoreceptor. To demonstrate the predicted actions of zatebradine, the authors measured the light response of rod horizontal cell after application of zatebradine. Zatebradine increased the response amplitude, delayed the time to peak and prolonged the response duration similar to that of in the stimulated response. Zatebradine also depolarized the resting potential of the rod horizontal, which cannot be explained by blocking ***Ih*** ***channels***.

L2 ANSWER 63 OF 68 MEDLINE DUPLICATE 37
ACCESSION NUMBER: 96359567 MEDLINE
DOCUMENT NUMBER: 96359567 PubMed ID: 8747199
TITLE: Mechanism of block by ZD 7288 of the hyperpolarization-activated inward rectifying current in guinea pig substantia nigra neurons in vitro.
AUTHOR: Harris N C; Constanti A
CORPORATE SOURCE: Department of Pharmacology, School of Pharmacy, London, United Kingdom.
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1995 Dec) 74 (6) 2366-78.
Journal code: 0375404. ISSN: 0022-3077.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19970203
Entered Medline: 19961009

AB 1. The effects of the novel bradycardic agent 4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride (ZD 7288) (Zeneca) were investigated on the hyperpolarization-activated cationic current (Ih) in guinea pig substantia nigra pars compacta neurons in vitro, using a single-microelectrode current-clamp/voltage-clamp technique. 2. Under current-clamp conditions, injection of large negative current pulses (0.1-0.5 nA, 400 ms) evoked a slow depolarizing "sag" in the electrotonic potential due to activation of the slow inward (anomalous) rectifier. In voltage-clamp recordings, hyperpolarizing voltage steps from a holding potential of -60 mV (close to resting potential) elicited slow inward current relaxations with kinetic properties similar to those seen for other neuronal Ihs. 3. ZD 7288 (10-100 μM) produced a consistent abolition of the electrotonic potential sag with no effect on membrane potential or spike properties. Under voltage clamp, Ih amplitude was clearly reduced in a time- and concentration-dependent manner (apparent half-maximum blocking concentration = 2 μM); full block of Ih was typically achieved after 10-15 min of exposure to 50 μM ZD 7288, with no significant recovery observed after 1 h of washing. 4. A similar (although more rapid) block of Ih was seen after application of 3-5 mM Cs⁺ (partially reversible after 30 min of washing). 5. Partial block of Ih by 10 μM ZD 7288 was accompanied by a reduction in the maximum amplitude

of the Ih activation curve, a small negative shift in its position on the voltage axis, and a linearization of the steady-state current-voltage relationship. The estimated Ih reversal potential, however, remained unaffected. 6. In 10 μM ZD 7288, the time course of Ih activation and deactivation was significantly slowed (within the range of -70 to -120 mV for the activation time constant and -70 to -90 mV for the inactivation time constant). 7. Blockade of Ih by ZD 7288 or Cs⁺ was independent of prior Ih activation (i.e., non-use dependent). 8. Intracellular loading with ZD 7288 also abolished the sag in the electrotonic voltage response and Ih relaxations, suggesting an intracellular site of action. By contrast, intracellular Cs⁺ had no effect on Ih properties. 9. Block of Ih by ZD 7288 (but not Cs⁺) was relieved by prolonged cell hyperpolarization, manifested as a slowly developing (half-time approximately 20 s) inward current at a holding potential of -100 mV. 10. We propose that ZD 7288, when applied externally, may behave as a "lipophilic" quaternary cation, capable of passing into the cell interior to block ***Ih*** ***channels*** in their closed state; this compound may thus prove a useful research tool, in place of Cs⁺, for studying the properties and significance of Ih currents in controlling neuronal function.

L2 ANSWER 64 OF 68 MEDLINE DUPLICATE 38
ACCESSION NUMBER: 95396558 MEDLINE
DOCUMENT NUMBER: 95396558 PubMed ID: 7545280
TITLE: Multiple ion binding sites in ***Ih*** ***channels*** of rod photoreceptors from tiger salamanders.
AUTHOR: Wollmuth L P
CORPORATE SOURCE: Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle 98195, USA.
CONTRACT NUMBER: GM-07108 (NIGMS)
NS-08174 (NINDS)
SOURCE: PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1995 May) 430 (1) 34-43.
Journal code: 0154720. ISSN: 0031-6768.
PUB. COUNTRY: GERMANY; Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 19970203
Entered Medline: 19951010

AB The mechanism of ion permeation in K⁺/Na⁺-permeable ***Ih*** ***channels*** of tiger salamander rod photoreceptors was investigated using the whole-cell voltage-clamp technique. ***Ih*** ***channels*** showed features indicative of pores with multiple ion binding sites: in mixtures of K⁺ and thallium (Tl⁺), the amplitude of the time-dependent current showed an anomalous mole fraction dependence, and K⁺ permeation was blocked by other permeant ions (with K_{0.5} values: Tl⁺, 44 μM; Rb⁺, 220 μM; NH₄⁺, 1100 μM) as well as by essentially impermeant ions (Cs⁺, 22 μM; Ba²⁺, 9200 μM) which apparently block Ih by binding in the pore. In contrast, Na⁺ had little blocking action on K⁺ permeation. The block by all of these ions was sensitive to external K⁺ with the block by Cs⁺ being the least sensitive. Na⁺ was more effective than K⁺ in reducing the block by Tl⁺, Rb⁺ and NH₄⁺, but was less effective for the block by Cs⁺ and Ba²⁺. The blocking action of Cs⁺ and Ba²⁺ was non-competitive, suggesting that they block ***Ih*** ***channels*** at independent sites. Based on the efficacy of block by the different ions, the degree to which K⁺ and Na⁺ antagonize this block and the noncompetitive blocking action of Cs⁺ and Ba²⁺, the permeation pathway of ***Ih*** ***channels*** appears to contain at least three ion binding sites with at least two sites having a higher affinity for K⁺ over Na⁺ and another site with a higher affinity for Na⁺ over K⁺.

L2 ANSWER 65 OF 68 MEDLINE DUPLICATE 39
ACCESSION NUMBER: 94277344 MEDLINE
DOCUMENT NUMBER: 94277344 PubMed ID: 7516499
TITLE: Specific bradycardic agents block the hyperpolarization-activated cation current in central neurons.
AUTHOR: Pape H C
CORPORATE SOURCE: Abteilung für Neurophysiologie, Medizinische Fakultät, Ruhr-Universität, Bochum, Germany.
SOURCE: NEUROSCIENCE, (1994 Mar) 59 (2) 363-73.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: ENGLAND; United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 19960129
Entered Medline: 19940721

AB A class of pharmacologically active substances, known as "specific bradycardic agents", exerts a negative chronotropic influence on cardiac activity, which heavily relies upon a potent blockade of the hyperpolarization-activated cation current in Purkinje fibers. Since the cation conductance activated by hyperpolarization seems to represent an ubiquitous class of membrane channel in mammals, the present study was undertaken to evaluate the influence of specific bradycardic agents [UL-FS 49 (zatebradine) and its derivative DK-AH 268] on excitable cells of the central nervous system. Thalamocortical relay neurons of the dorsolateral geniculate nucleus, prepared from the guinea-pig thalamus as in vitro slices, were taken as model cells, because the significance of the hyperpolarization-activated cation current (Ih) for electrogenic activity is well documented in these neurons. Local application to relay neurons of the bradycardic agents at concentrations in the range 10(-5) to 10(-3) M resulted in a significant reduction in the amplitude of the Ih current, in the amplitude of the Ih activation curve, and in the slope of the fully activated Ih I/V-relationship. The bradycardic agents did not affect the instantaneous currents with no contribution of Ih, the time course of Ih activation, the voltage range of Ih activation, or the reversal potential of Ih. The inhibitory effect was critically dependent upon Ih activation with open ***Ih*** ***channels*** probably representing a sufficient condition for blockade. Significant recovery from block did not occur. Under current-clamp conditions, slow anomalous inward rectification of the membrane in the hyperpolarizing direction was blocked, and the resting input resistance increased by 30% associated with a negative shift (average 10 mV) of the membrane potential into a region of Ca(2+)-mediated burst activity. Parameters of electrophysiological activity outside the range of Ih activation were not significantly affected. These data indicate a selective and use-dependent blockade exerted by specific bradycardic substances on the conductance underlying Ih with no alteration in the gating properties. In view of the existence of hyperpolarization-activated cation conductances in neurons from various regions of the mammalian peripheral and central nervous systems, the results of the present study remind us of possible neuronal side-effects of bradycardia-producing agents.

L2 ANSWER 66 OF 68 MEDLINE DUPLICATE 40
 ACCESSION NUMBER: 93115693 MEDLINE
 DOCUMENT NUMBER: 93115693 PubMed ID: 1282144
 TITLE: Ionic selectivity of ***Ih*** ***channels*** of rod photoreceptors in tiger salamanders.
 AUTHOR: Wollmuth L P; Hille B
 CORPORATE SOURCE: Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle 98195.
 CONTRACT NUMBER: GM-07108 (NIGMS)
 NS-08174 (NINDS)
 SOURCE: JOURNAL OF GENERAL PHYSIOLOGY, (1992 Nov) 100 (5) 749-65.
 Journal code: 2985110R. ISSN: 0022-1295.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199302
 ENTRY DATE: Entered STN: 19930219
 Last Updated on STN: 19970203
 Entered Medline: 19930201

AB Ionic selectivity of ***Ih*** ***channels*** of tiger salamander rod photoreceptors was investigated using whole-cell voltage clamp. Measured reversal potentials and the Goldman-Hodgkin-Katz voltage equation were used to calculate permeability ratios with 20 mM K+ as a reference. In the absence of external K+, Ih is small and hard to discern. Hence, we defined Ih as the current blocked by 2 mM external Cs+. Some small amines permeate ***Ih*** ***channels***, with the following permeability ratios (PX/PK): NH4+, 0.17; methylammonium, 0.06; and hydrazine, 0.04. Other amines are totally impermeant: dimethylammonium (< 0.02), ethylammonium (< 0.01), and tetramethylammonium (< 0.01). When K+ is the only external permeant ion and its concentration is varied, the reversal potential of Ih follows the Nernst potential for a K+ electrode. ***Ih*** ***channels*** are also permeable to other alkali metal cations (PX/PK): Tl+, > 1.55; K+, 1; Rb+, > 0.55; Na+, 0.33; Li+, 0.02. Except for Na+, the relative slope conductance had a similar sequence (GX/GK): Tl+, 1.07; K+, 1; Rb+, 0.37; NH4+, 0.07; Na+, 0.02. Based on permeabilities to organic cations, the narrowest part of the pore has a diameter between 4.0 and 4.6 A. Some permeant cations have large effects on the gating kinetics of ***Ih*** ***channels***; however, permeant cations appear to have little effect on the steady-state activation curve of ***Ih*** ***channels***. Lowering K+ or replacing K+ with Na+ reduces the maximal conductance of Ih but does not shift or change the steepness of its voltage dependence. With ammonium or methylammonium replacing K+ a similar pattern is seen, except that

there is a small positive shift of approximately 10 mV in the voltage dependence.

L2 ANSWER 67 OF 68 SCISEARCH COPYRIGHT 2002 ISI (R)
 ACCESSION NUMBER: 92:40587 SCISEARCH
 THE GENUINE ARTICLE: GY440
 TITLE: MECHANISM OF ION PERMEATION IN ***Ih*** ***CHANNELS***
 AUTHOR: WOLLMUTH L P (Reprint); HILLE B
 CORPORATE SOURCE: UNIV WASHINGTON, DEPT PHYSIOL & BIOPHYS, SEATTLE, WA, 98195
 COUNTRY OF AUTHOR: USA
 SOURCE: FASEB JOURNAL, (01 JAN 1992) Vol. 6, No. 1, pp. A289.
 ISSN: 0892-6638.
 DOCUMENT TYPE: Conference; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: ENGLISH
 REFERENCE COUNT: No References

L2 ANSWER 68 OF 68 MEDLINE DUPLICATE 41
 ACCESSION NUMBER: 83272878 MEDLINE
 DOCUMENT NUMBER: 83272878 PubMed ID: 6878006
 TITLE: Does the "pacemaker current" generate the diastolic depolarization in the rabbit SA node cells?
 AUTHOR: Noma A; Morad M; Irisawa H
 SOURCE: PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1983 May) 397 (3) 190-4.
 Journal code: 0154720. ISSN: 0031-6768.
 PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198309
 ENTRY DATE: Entered STN: 19900319
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 AB Small preparations of spontaneously beating rabbit sino-atrial node (SA node) were voltage clamped with the two-microelectrode technique. The effects of 0.25-5 mM Cs+ on the spontaneous pacing rate and the time-dependent inward "pacemaker" current, ih, were studied. In the presence of 2 mM Cs+, the spontaneous pacing rate decreased only slightly even though ih was strongly depressed at potentials negative to -60 mV Cs+ had little or no effect on other time-dependent currents observed with clamp pulses less negative than -50 mV. Since no voltage-dependence to the Cs+ effect on ih could be measured (between -90 mV and -20 mV), it was considered unlikely that the lack of Cs+ effect on the rate of diastolic depolarization results from a voltage-dependent effect of Cs+ on the ***ih*** ***channel***. Adrenaline produced a marked positive chronotropic effect in Cs+-treated SA node cells. This effect was accompanied by marked enhancement of the slow inward current (isi) with no change in the Cs+-blocked ih current. These results are consistent with the idea that ih plays a minor role in generation of pacemaker depolarization, and suggest a more prominent role of isi in the generation of diastolic depolarization in SA nodal cells.